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THE VEGETATIVE NERVOUS SYSTEM

AN INVESTIGATION OF THE MOST RECENT ADVANCES

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WALTER TIMME, M.D.
THOMAS K. DAVIS, M.D.
HENRY ALSOP RILEY, M.D.

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LIST OF CONTRIBUTORS TO VOLUME IX

ADSON, ALFRED W., M.D., M.S., F.A.C.S. (p. 721)
Associate Professor of Surgery, Mayo Foundation for Medical Education and Research, Graduate School of Medicine, University of Minnesota; Head of Section on Neurologic Surgery, Mayo Clinic, Rochester, Minnesota

BARD, PHILIP, A.M., PH.D. (p. 67)
Assistant Professor of Physiology, Princeton University, Princeton, New Jersey

BEATTIE, JOHN, M.D., D.Sc. (p. 249)
Associate Professor of Anatomy, McGill University, Montreal

BRICKNER, RICHARD, M., M.D., F.A.C.S. (p. 542)
Assistant Neurologist City Hospital, Neurological Institute and Vanderbilt Clinic, New York City

BROW, G. R., M.D.C.M. (p. 249)
Assistant in Medicine, Royal Victoria Hospital: Research Associate, McGill University Medical Clinic, Montreal

BROWN, GEORGE E., M.D., F.A.C.P. (p. 721)
Associate Professor of Medicine, Mayo Foundation for Medical Education and Research, Graduate School of Medicine, University of Minnesota; Associate in Section of Medicine, Mayo Clinic, Rochester, Minnesota

CANNON, WALTER B., A.M., M.D., S.D., LL.D. (p. 181)
George Higginson Professor of Physiology, Harvard Medical School, Boston

COBB, STANLEY, M.D. (p. 458)
Professor of Neuropathology, Harvard Medical School; Visiting physician for Neurology, Boston City Hospital, Boston

CRAIG, C. BURNS, M.D. (p. 569)
Physician, Neurological Institute; Neurologist, Fordham Hospital; Chief of Neurological Clinic, Vanderbilt Clinic, New York City

CRAWFORD, J. HAMILTON, M.D. (p. 343)
Associate in Physiology and Medicine, Long Island College Hospital, Brooklyn

CRILE, GEORGE W., M.D. (p. 624)
Professor Emeritus of Surgery, Western Reserve University School of Medicine; Chief of the Cleveland Clinic, Cleveland

CROSBY, ELIZABETH C., PH.D. (p. 199)
Associate Professor of Anatomy, University of Michigan, Medical School, Ann Arbor, Michigan

DUKE, WILLIAM W., M.D. (p. 499)
Kansas City, Missouri

FORBES, ALEXANDER, M.D. (p. 317)
Associate Professor of Physiology, Harvard Medical School, Boston

FRANTZ, ANGUS MACDONALD, M.D. (p. 46)
Associate in Neurology, College of Physicians and Surgeons, Columbia University; Associate Attending Neurologist, Neurological Institute; Attending Neurologist, New Jersey Orthopaedic Hospital, Orange; Assistant Attending Neurologist, City Hospital, New York City

HASSIN, GEORGE B., M.D. (p. 437)
Professor of Neurology, University of Illinois College of Medicine, Chicago

HINES, MARION, PH.D. (p. 124)
Associate in Anatomy, Johns Hopkins Medical School, Baltimore

HINSEY, JOSEPH, C., PH.D. (p. 153)
Associate Professor of Neuroanatomy, Institute of Neurology, Northwestern University Medical School, Chicago

HOSKINS, ROY G., M.D., PH.D. (p. 352)
Research Associate in Physiology, Harvard Medical School, Boston

HUBER, G. CARL, M.D. (p. 199)
Professor of Anatomy and Director of the Anatomic Laboratories; Dean of the Graduate School, University of Michigan, Ann Arbor, Michigan

HUGHSON, WALTER, M.D. (p. 468)
Johns Hopkins University, Baltimore

KERR, HARRY HYLAND, M.D. (p. 766)
Professor of Neuro-Surgery, George Washington University Medical School, Washington, D. C.

KESSEL, LEO, M.D. (p. 538)
New York City

KUNTZ, ALBERT, PH.D., M.D. (pp. 13; 100)
Professor of Anatomy, St. Louis University School of Medicine, St. Louis

LEE, FERDINAND C., M.D. (p. 417)
Assistant Resident Surgeon, Johns Hopkins Hospital, Baltimore

LEE, MILTON O., PH.D. (p. 352)
Research Fellow in Physiology, Harvard Medical School, Boston

LINDSAY, JANVIER, W., M.D. (p. 778)
Washington, D. C.

LONG, C. N. H., M.SC., M.D.C.M. (p. 249)
Assistant Professor in Medical Research, McGill University, and Research Associate, McGill University Medical Clinic, Montreal

MALONE, EDWARD F., M.D. (p. 92)
Professor of Anatomy, University of Cincinnati

MOORE, ROBERT M., M.D. (p. 385)
National Research Fellow in Medical Sciences, Harvard Medical School, Boston

NONIDEZ, JOSÉ F., SC.D. (p. 366)
Associate in Anatomy, Cornell University Medical College, New York City

PATTEN, CLARENCE A., M.D. (p. 479)
Assistant Professor of Neurology, Graduate School of Medicine, University of Pennsylvania, Philadelphia

PEET, MAX MINOR, M.S., M.D., F.A.C.S. (p. 633)
Professor of Surgery, University of Michigan Medical School; Chief of Neuro-Surgery, University Hospital, Ann Arbor, Michigan

PENFIELD, WILDER, M.D., B.SC. OXON. (p. 645)
Professor of Neurological Surgery, McGill University; Surgeon in Charge of Neurological Surgery, Royal Victoria Hospital and Montreal General Hospital, Montreal

POTTENGER, FRANCIS M., M.D. (p. 587)
Chief of the Pottenger Sanatorium, Monrovia, California

RANSON, STEPHEN W., M.D. (p. 394)
Professor of Neurology, Northwestern University Medical School, Chicago

Reid, Mont R., M.D., (p. 690)
Associate Professor of Surgery, University of Cincinnati College of Medicine; Assistant Director, Surgical Service, Cincinnati General Hospital and Children's Hospital, Cincinnati

Rice, E. Clarence, M.D. (p. 778)
Washington, D. C.

Selinger, Maurice A., M.D. (p. 778)
Associate Clinical Professor of Medicine, Georgetown University School of Medicine, Washington, D. C.

Timme, Walter, M.D. (p. 1)
Professor of Clinical Neurology, College of Physicians and Surgeons, Columbia University; Senior Attending Neurologist, Neurological Institute, New York City

Warthin, Aldred Scott, Ph.D., M.D., LL.D. (p. 664)
Professor of Pathology and Director of the Pathological Laboratories, University of Michigan Medical School, Ann Arbor, Michigan

White, James C., M.D. (p. 786)
Instructor in Snrgery, Harvard Medical School; Associate in Surgery, Massachusetts General Hospital, Boston

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PREFACE

IT IS with great satisfaction that the Association for Research in Nervous and Mental Disease now puts forth this volume—the ninth of the Series—embodying the results of research into the problems and difficulties presented by the vegetative nervous system. Satisfaction, because of the authoritative weight of the opinions and conclusions of the eminent contributors to the subject whose presence and discussions at the meeting made it one of the notable scientific gatherings of the year. The embodiment of their work in this field, with mutual constructive criticism in the form of query and reply on moot or doubtful or difficult phases of their research investigations, forms the present volume.

The difficult work of collecting, arranging and editing the mass of material was the labor of our Editorial Board, Dr. Henry Alsop Riley and Dr. Thomas K. Davis. Much appreciation is also due to Miss Josephine R. Bates for her painstaking care in the editorial work. To them, as well as to the members of the Commission who gave much valuable time and energy in making the meeting an event and this volume a success, the thanks of the Association are due. Readers of this volume will find in it the most recent work in the field of vegetative neurology presented by the masters of the subject, each in his individual style; and, added to this, elucidatory questions, answers and criticisms thereon. May we hope that it will inform, interest and instruct.

W. T.

December 13, 1929.

Section I

HISTORICAL RETROSPECT

CHAPTER I

THE VEGETATIVE NERVOUS SYSTEM

Historical Retrospect

WALTER TIMME, M.D.

IN THESE, for us, modern times, the term "vegetative nervous system" seems to imply a more or less crystallized conception of a nervous mechanism devoted to the control, co-ordination and adaptation of the functions exercised by smooth muscle-fiber and glandiferous tissues, with subsidiary systems in the viscera. This conception is of quite recent origin and is due to the intensive labors of such investigators as Langley (30), Gaskell (16) and their schools and co-workers.

The development to the present intricate levels, however, was slow in the making. The early anatomists, preceding the seventeenth and sixteenth centuries, recognized the outstanding difference between the sympathetic nerve and all other nerves of the body in that it had little masses or ganglia situated along its entire course. They also knew that the heart and intestines were supplied by nerves arising from these ganglia. Because these ganglia were evident practically along its entire course to the cranium, they supposed that the sympathetic nerve arose from the brain-tissue in the neighborhood of the vagus nerve, and passing down the spinal column, was thence distributed to the body.

In the early eighteenth century du Petit (36) stated, "Les nerfs intercostaux fournissent des rameux qui portent des esprits dans les yeux"; and opposed the doctrine that the nerve-current passed down from the brain, by advancing the fact that stimulation of the cervical sympathetic nerve caused the eyes to become lively and active and the pupils to become dilated. Somewhat later, Winslow (39) showed that the nerves emanating from the superior cervical ganglion toward the cranial nerves *diminished in caliber;* hence the conclusion was draw that this could not be consonant with the fact of their cranial origin. His opinion was that the ganglia were "little brains" of the sympathetic system and represented centres of origin of this system. He it

was who introduced the name "sympathetic" as descriptive of the system because he believed the "sympathies" of the body were under its control. The name "involuntary nervous system" was applied even earlier than this; and although Gaskell (16) in recent times adopted this term himself, yet it is not quite apt, for there are involuntary nerves even in the so-called voluntary system.

In 1764, Johnstone (22) evolved a theory that voluntary movements are converted into involuntary movements in the ganglia of the sympathetic nervous system; and hence involuntary movements are controlled by ganglionic nerves. These involuntary movements were not confined to nerves supplying the viscera only, but also to nerves concerned with involuntary movements of skeletal muscles as well, such as tremors, spasms and others. The ganglia of the cerebrospinal system were, therefore, also included. Somewhat later, however, when it was found that the cerebrospinal ganglia belong to afferent nerves, they were excluded from the category of the ganglionated system. Haller's (20) discovery that there are nerve-fibers of communication from the ganglia of the sympathetic chain to the spinal nerves, revealed an association between the cerebrospinal system and the sympathetic, which had not been previously considered at all, and revealed the sympathetic system in quite a new rôle.

The term "vegetative nervous system" was introduced originally into medical literature by Bichat in 1800 (2). According to his conception of the nervous mechanism it was analogous to the biological make-up of the individual, namely, it was divided into two distinct parts: to the one, concerned entirely with environment, to which it adapted itself by means of the voluntary muscles of locomotion and the external organs of sense, he gave the name "animalic" (*vie de relation*); and to the other, concerned entirely with the nutritional functions of the body, he gave the name "vegetative" or "organic" (*vie de nutrition*). And so were introduced the terms "animal" and "vegetable" nerves. The ganglia of the great sympathetic chain and some of the cranial nerves formed the nervous organs of *vegetative* or organic life, and regulated and controlled it; whereas the cerebrospinal system regulated and controlled the life "*animalic*."

This conception stimulated much discussion and was by some authors enthusiastically received. Closer comparisons were drawn between the two systems; thus, the sympathetic chain of ganglia was compared with the spinal cord, and the celiac ganglion with the brain, as the

centre of the system. Because of its anatomical location this ganglion was considered the centre of a system particularly concerned with the regulation of the abdominal organs and glands.

This hypothesis of Bichat's, however, was never entirely accepted and all its terms gradually fell into disuse, except the term "*vegetative*" which gradually dominated all others applied to the entire autonomic system.

In 1838, Remak (37) published his discovery of the non-medullated fibers of the sympathetic system as quite distinct from the medullated nerves of the cerebrospinal system. Soon after, Joh. Müller (33) predicated from the fact that the rami communicantes contained both white and gray fibers, that the former were cerebrospinal in origin and the latter sympathetic maintaining a reciprocal relationship between both systems; the "animalic" fibers conducting impulses to the "vegetative" centres and the vegetative fibers impulses to the animalic centres. These two discoveries, by Remak and by Müller, seemed to substantiate the theory of Bichat's as to the independent existence of the two nervous systems. Bichat's contentions held more or less sway until the conclusions based upon the experimental research of three independent investigators, Beck, Gaskell and Ónodi, showed conclusively from three different angles, that the sympathetic system did not have the independence from the cerebrospinal system that Bichat believed.

T. S. Beck in 1846 (1) gave evidence that all the non-medullated fibers passing in towards the spinal cord were peripheral in character and not central.

A. D. Ónodi (35) stated that if there were two independent nervous systems, *animalic* and *vegetative*, one being peripheral and the other central, there ought to be logically two separate origins for them. He showed that the groups of cells which form the sympathetic chain originated from a mass of cells close to the central nervous system and that the remainder of this mass formed the posterior root ganglion, thus proving that the sympathetic cells were in the first place a part of the cerebrospinal system, but had migrated farther than the posterior root ganglia.

In 1889, W. H. Gaskell (14) cut serial sections through the rami communicantes and through the roots of the spinal segmental nerve after treatment with osmic acid and found "that the main mass of the non-medullated fibers, after entering the spinal segmental nerve

turned towards the periphery along the nerve, but that a smaller number proceeded along the roots towards the spinal cord." On tracing the latter, which especially went along the posterior root, he found that they passed off into the membranes around the spinal cord to supply the blood-vessels; none entered into the spinal cord itself. It was perfectly evident, therefore, that the reciprocal connection between the two systems did not exist; that in fact, all the characteristic non-medullated sympathetic nerve-fibers—wherever found—are peripheral nerves. And he added that incidentally an observation by Valentine "that stimulation of posterior roots caused constriction of the blood vessels of the dura mater," was explained.

These three investigators thus riddled the Bichat theory and showed, furthermore, that there was only one system of communication between the animalic and the vegetative nervous systems, namely, the white rami communicantes.

Because of the beginning of the confusion in the terms now applied in the nomenclature to the various parts of the vegetative, or organic, system, Dastre and Morat (4) proposed to return to the term "sympathetic nervous system" of Winslow; but by virtue of their own investigations, decided to add thereto certain branches of the fifth, seventh, ninth and tenth cranial nerves. This proposition, of course, awakened no end of controversy, which it is safe to say has not yet been entirely settled. The term "involuntary nervous system" adopted by Gaskell (16) and others, and "autonomic" by Langley (30) and his school, are even to this day competing with "vegetative nervous system" originally proposed by Bichat.

W. H. Gaskell (6–11, 13, 17) at this time was probably the most profound scientist who occupied himself with the medical problems of the "involuntary nervous system." As a result of his investigations he was enabled to show at first that the central nervous system supplies efferent fibers in the white rami communicantes to the main sympathetic chain only in the *thoracicolumbar region.* Then he came to the conclusion in 1885 (12) that the sympathetic nervous system consists largely, if not entirely, of a system of motor cells situated on the path of the efferent fibers from the spinal cord to the peripheral organ; that in fact both roots may be looked upon as ganglionated, the anterior as well as the posterior. He held that these motor cells represent the terminal neurones of the efferent system, just as the sensory cells of the posterior root ganglia represent the terminal cells of the afferent

system; the difference between the two sets being the fixed position of the latter on the posterior roots near the spinal cord, and the vagrant character of the former at various distances from the cord.

In these conclusions he was supported by the experiments of Langley and Dickinson in 1889 with nicotine (31). They showed that nicotine injections prevented the effect of stimulation of the fibers from the spinal cord which go to the sympathetic ganglia via the rami communicantes, but did not affect the fibers from the sympathetic ganglia onwards. That is to say, the action of nicotine prevented the stimulation from proceeding beyond the sympathetic cell to its fibers. These spinal fibers—the small medullated ones from the cord to the sympathetic ganglion—Langley named "preganglionic," and the non-medullated sympathetic fibers themselves "postganglionic."

Gaskell frequently reiterated his conviction, in which Langley agreed with him, that the motor nerve-cells and the sensory nerve-cells at one period formed a single mass of cells in the position of the posterior root ganglion; and then, as growth went on, the motor, or sympathetic, mass separated from the original mixed group and became more and more vagrant, while the sensory mass remained stationary just outside the spinal cord, as the posterior spinal root ganglion. Indeed in some lower forms (tortoise) the ramus communicans in the thoracic region springs directly out of this posterior root ganglion. Giacomini stated (18) that in the toad and the bee the two ganglia are in actual contact. The fact that the sympathetic system of cells, said Gaskell, has split off from a cell-mass in the position of the posterior root ganglion, has led many to look upon the sympathetic ganglia as offshoots mainly sensory in function. Langley's work, however, made it clear that only the motor cells have passed towards the periphery, while the sensory cells of the system have remained in their original position in the posterior root ganglion.

Of modern investigators, Kuntz (23–27) disagreed with this view, maintaining that the origin of the sympathetic ganglia is largely from the anterior roots of the spinal cord and based his view upon exhaustive animal and embryological experimentation. He, in turn, was taken to task by Erik Müller and Sven Ingvar (32), who by means of experimental work upon the embryos of selachians and frogs came to the directly opposite conclusion from Kuntz; and decided that the sympathetic cells were developed embryologically from the posterior spinal ganglia, agreeing herein with Held (21) and with Gaskell (15,

16). Langley (28, 29) also proved that the commissural fibers and relays of cells are connected with one another and are found as a characteristic of the central nervous system; that they do not exist in the sympathetic system and, hence, the analogy between the two systems is not in reality a true one.

Langley objected to the old terms "organic" and "animalic" in his discussion of the so-called sympathetic nervous system, and substituted, therefore, the term "autonomic" for *organic* or *vegetative.* Gaskell found fault as well with "autonomic" and proposed, because the question was concerned with a nervous system controlling the functions of special tissues not directly under the control of the will, the term "involuntary nervous system," in contradistinction to the voluntary nervous system. And yet, even here there are objections; for in the so-called voluntary nervous system many involuntary effects appear, and hence the apposition is not a strictly true one.

Gaskell not only determined that there is no outflow to the sympathetic nervous system above the thoracic level but also that the lower level of such outflow was limited by the lumbosacral plexus. He arrived at this conclusion by virtue of the fact that no white rami communicantes exist beyond these limits. Later, he added the observation that again in the sacral section—the anterior roots of the second and third sacral nerves—there is again a mass of the fine medullated fibers. These he traced, not to the ganglia of the sympathetic chain, but to separate sets of ganglia lying on the surface of the bladder and rectum. These fibers he found passed directly to the ganglion-cells without in any way being connected with the main or lateral chain of the sympathetic ganglia. This sacral outflow he finally designated, following Langley, the "pelvic nerve."

Employing this method, he next examined all the anterior roots above the dorsal region for the fine medullated fibers as before, and found no trace of them in any of these cervical roots. But these cervical segments have *three roots*, not two,—a dorsal, a ventral *and a lateral root.* In the lateral roots (which form the spinal accessory nerve) Gaskell (12, 14, 16) again found evidences of the fine medullated fibers. Tracing these to their destination, he found that they all passed into the internal branch of the spinal accessory *to join the vagus nerve*, leaving the main branch a purely motor nerve. Here then he demonstrated a cranial outflow, via the vagus, of the same kind of fiber as those in the thoracicolumbar and sacral regions. Further

investigation showed him that such nerves as the chorda tympani and the great superficial petrosal (running from the facial to Meckel's ganglion) were also of the nature of rami communicantes in their structure. To this cranial outflow of connector nerves he gave the name "bulbar" outflow. Anterior to the bulbar outflow his investigations showed him the fine medullated fibers in the roots of the oculomotor nerve passing to the ciliary ganglion. This outflow he denominated the "midbrain" outflow.

To summarize: Gaskell's (15, 16) great achievement was to show that the *involuntary* nervous system is built up on the same plan as the *voluntary* system, with receptor, connector and excitor elements. The marked difference is that the excitor elements have left the central nervous system and become peripheral, forming the various ganglia found throughout the body; while the receptor elements have remained in the same position as those of the voluntary system, namely, in the posterior root ganglion, and connect by means of sensory root fibers with the cells of the connector elements which have remained in the central nervous system. The connector fibers have passed out to reach their respective, peripherally-situated excitor elements. This outflow of connector fibers does not occur, in the higher vertebrates, in every segment, but is interrupted at the places where the nerve-plexuses for the upper and lower limbs come in. Hence there may be considered three outflows of these fibers: (*a*) a bulbar, (*b*) a thoracico-lumbar, (*c*) a sacral. In addition, a fourth small group exists, confined to the region of the midbrain, which connects with the excitor neurones forming the ciliary ganglion.

In addition to this exposition of the involuntary nervous system, Gaskell also classified the ganglion groups into two: (*a*) the ganglia lying along the vertebrae on each side,—the *vertebral* or lateral ganglionic chain; and (*b*) ganglionic masses lying on each side of the abdominal aorta, which form the *prevertebral* or collateral ganglia. He determined also that the blood-vessels of the extremities, and perhaps others as well, are innervated not only by visceral nerves, but also receive dilator fibers by means of somatic nerves.

Towards the end of the nineteenth century (1898) several views of the "involuntary" nervous system obtained ((30), pp. 8–14). One was that the smooth muscle-fibers and glands were supplied not only by this system but also by the cerebrospinal system. Secondly, the involuntary nervous system was regarded as separated into three

distinct parts anatomically. It was known that the thoracicolumbar portion supplies the entire body; while the craniobulbar and sacral, only parts of the body. It was also known, due largely to Langley and his co-workers, that the thoracicolumbar portion functions in opposition to the craniobulbar and the sacral. Langley regarded the sympathetic, namely, the thoracicolumbar portion of the system, as distinct from the rest of his "autonomic system"; and recognized also that the outflow supplying the eye is distinct from the rest of the cranial outflow. His divisions of the entire system were: (*a*) tectal, (*b*) bulbosacral, (*c*) sympathetic.

Later, because of the effects of adrenalin (1905) on the various parts of this system ((30), pp. 29–35), he classified the similarly affected divisions, namely, the tectal and bulbosacral, into one group which he called the "parasympathetic" system. Furthermore, he added the "enteric" nervous system to the others (30). This was composed of the various individual specific plexuses in the viscera—such as the Auerbach and Meissner plexuses. While Schilf (38) proposed that in deference to Langley, the nomenclature devised by him be retained, and the entire system be denominated "autonomic," yet this term at the present time has given way on the Continent and in America largely to the term "vegetative" for the entire system, while "sympathetic" and "parasympathetic" are retained for its component parts.

During the present century the pharmacology of the vegetative nervous system has occupied physiologists throughout the world,—for its various portions react specifically to different pharmaceutical agents and in contrary ways. On the basis of such differences in action, Eppinger and Hess (5) have endeavored to demonstrate a series of real, basic-system disturbances. If the parasympathetic system is unduly sensitive and responsive to stimuli, the condition known as "vagotonia" is said to exist; and it is recognized by the overactivity of the functions controlled by the parasympathetic nervous system. If the sympathetic division is the one that is oversensitized, then the condition of "sympathicotonia" presents itself. Normally these two great divisions of the vegetative nervous system are always mutually balanced with more or less opposite effects in the tissues they supply—the sympathetic catabolic in its activities, the parasympathetic anabolic. Later, Guillaume (19) advanced a theory of "neurotonie" combining various phases of vagatonia and sympathicotonia and including in his category almost all the ills that

human kind suffers which had heretofore gone under the terms of the neuro-cardio-psycho-neuroses.

In 1915, Cannon (3) gave evidence of the bodily changes that take place in pain, hunger, fear and rage. These changes are intermediated by the divisions of the vegetative nervous system passing to the peripheral and to their terminal endings in the viscera; the emotions arising originally in the cerebrum and giving rise to the disturbances in the vegetative system via the connector fibers between the central nervous system and the vegetative. The terminal effects are the widening of the pupil, erection of pilomotor fibers, changes in the secretions of stomach and intestines, changes in the blood-pressure, secondary effects due to the release of adrenin by virtue of the stimulation of the adrenal glands by the splanchnic nerves, etc.,—and all of these changes are purposeful and helpful to the individual. From these initial investigations by Cannon and his collaborators, and based upon them, many fanciful and largely unwarranted hypotheses especially in the realm of the neuroses, psychoneuroses and psychoses have arisen. Indeed, the sympathetic, or rather the vegetative nervous system, from being represented in the text-books of anatomy of a generation ago to the extent of four or five pages in a volume of over a thousand pages, has now arrived at the all engrossing level at which it and its divisions are called "die Lebensnerven" (L. R. Müller (34)), and no illness or indisposition, no functional disturbance, no mental or nervous aberration can well be explained without having recourse to the illuminating results of investigation and research into the activities of the Vegetative Nervous System.

The present program, on which will be found the names of the greatest workers extant in this field of medicine, will endeavor to show the advances that are still being made in this all-absorbing study and we hope that it will prove a landmark in the progress of our investigation.

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Section II

MORPHOLOGY

CHAPTER II

DEVELOPMENT OF THE AUTONOMIC NERVOUS SYSTEM[1]

ALBERT KUNTZ, M.D.

HISTORICAL SURVEY

AS EARLY as 1847 Remak (57) described the primordia of the sympathetic trunks in embryos of the chick as ganglionic enlargements on the communicating rami, situated near the points at which the latter deviate from the spinal nerves. He advanced the theory that the cells which give rise to the sympathetic ganglia are differentiated *in situ* from mesodermal tissue. This theory held undisputed sway for nearly three decades. It was advocated by Goette (23) in 1875, and still adhered to by him at a much later date. As early as 1877 Balfour (3) pointed out clearly that the autonomic system is derived from the cerebrospinal nervous system. Later investigators in this field, with few exceptions, have supported Balfour's view. The older theory of the mesodermal origin of the sympathetic ganglia was advocated by Paterson (55), Fusari (16, 17), and Camus (8). Dart and Shellshear (12) also advocated this theory in a somewhat modified form. Still more recently Tello (63) again advocated the theory that the sympathetic ganglia are differentiated *in situ* and that the cells which become incorporated in them are derived from the mesoderm.

The work of Balfour marks the beginning of the modern conception of the ectodermal origin of the autonomic nervous system and its genetic relationship to the cerebrospinal nervous system. He described the primordia of the ganglia of the sympathetic trunks in elasmobranch embryos as simple enlargements on the spinal nerve-trunks which are subsequently displaced toward the aorta, each, however, retaining connection with its respective nerve by a fibrous branch which becomes the communicating ramus.

The following year (1878) Schenck and Birdsall (60) extended Balfour's conception in a somewhat modified form to the higher verte-

[1] From the St. Louis University School of Medicine.

brates. They observed, in embryos of birds and mammals, that cells become displaced from the distal ends of the spinal ganglia into the spinal nerve-trunks, and advanced the theory that these cells become incorporated in the primordia of the sympathetic ganglia. They did not, however, clearly describe the process by which these cells are displaced from the spinal ganglia into the sympathetic primordia.

In 1886, Önodi (54) also described the primordia of the sympathetic trunks and prevertebral ganglia, in embryos of various vertebrates, as made up of cells which become displaced from the spinal ganglia. He advanced the theory that cells are forced peripherally from the distal ends of the spinal ganglia by the pressure which is exerted by the newly formed elements back of them. His, Sr. (25–27), also observed the displacement of cells from the distal ends of the spinal ganglia in human embryos. He described these cells as germinal cells which break through the ventral roots of the spinal nerves and migrate toward the future location of the sympathetic trunk. Shortly after this, His, Jr. (28, 29), also described the active migration of cells from the spinal ganglia into the primordia of the sympathetic trunks in embryos of the chick. He traced these cells along the paths of the spinal nerves and communicating rami.

Marshall (50), in 1893, described the primordia of the sympathetic trunks in embryos of the frog and chick as a series of outgrowths from the spinal nerves, which develop into ganglionic enlargements and later become connected with each other by longitudinal commissures. Several years later, Hoffmann (32), who had previously (31) confirmed Balfour's findings in elasmobranch embryos, described the primordia of the sympathetic trunks in embryos of certain of the Urodela as consisting of scattered cells along the dorsolateral aspects of the aorta, some of which are connected with the communicating rami by slender protoplasmic processes.

The differences of opinion expressed by these early investigators, regarding the method by which cells are displaced into the sympathetic primordia, may be accounted for at least in part by differences in the morphogenesis of the sympathetic trunks in the several classes of vertebrates. In the Elasmobranchii, the primordia of the sympathetic trunks arise as ganglionic enlargements on the spinal nerves (Balfour (3), van Wijhe (65)). In the Amphibia, they arise as aggregates of cells lying along the dorsolateral aspects of the aorta after fibers have appeared in the communicating rami (Hoffman (32), Neu-

mayer (53)). In birds, the primary sympathetic trunks, which arise as columns of cells lying along the dorsolateral aspects of the aorta, early give way to the secondary sympathetic trunks, the primordia of which arise as aggregates of cells situated just mesial to the ventral roots of the spinal nerves (His, Jr. (28)). In mammals, the primordia of the sympathetic trunks arise as aggregates of cells lying along the dorsolateral aspects of the aorta (His, Sr. (27), Kohn (33)). The influence of these differences in the morphogenesis of the sympathetic trunks upon the interpretation of the observations at hand, becomes obvious when it is borne in mind that the theory advanced by Ónodi was based on his findings in elasmobranch embryos, while the theory of the active migration of cells into the sympathetic primordia, as advanced by His, Sr. and His, Jr., was based mainly on observations made on embryos of birds and mammals.

Kohn (33, 34), who studied the development of the sympathetic trunks in embryos of the rabbit, advanced the theory that the primordia of the sympathetic ganglia are composed of cells which arise by the proliferation of elements which have not advanced peripherally from the spinal ganglia, but which were differentiated *in situ* in the spinal nerves. According to this theory, embryonic neurocytes deviate from the course of the spinal nerves toward the aorta and by nuclear division give rise to syncytial communicating rami, from the distal ends of which groups of cells become separated and give rise to the sympathetic ganglia. Neumayer (53), who made his observations on embryos of the Lacerta and of the chick, also traced the origin of the sympathetic trunks directly to the spinal nerves. He advanced the opinion that the sympathetic primordia arise, in all vertebrates, from cells which are differentiated *in situ* in the dorsal and ventral nerve-roots. The views of both Kohn and Neumayer, probably, were influenced by their allegiance to the theory of local differentiation and the multicellular nature of nerve-fibers.

The work of Froriep (15), based on embryos of the torpedo and of the rabbit, marks a decided advance in the knowledge of the histogenesis of the sympathetic ganglia. Like a number of other investigators before him, he had previously observed cells of medullary origin in the ventral roots of the spinal nerves, but was able in 1907 to present definite observations which he interpreted as indicating that cells of medullary origin advance peripherally along the ventral nerve-roots and enter the primordia of the sympathetic trunks. He suggested

that it is mainly these cells which become differentiated into neurones in the sympathetic ganglia. Cajal (6) also expressed the opinion that the sympathetic neurones are essentially motor cells derived from the spinal cord.

Held (24) and Marcus (49) both continued to advocate the older theory and vigorously attacked the work of Froriep. They supported the view that the cerebrospinal ganglia constitute the sole source of the cells which enter the primordia of the sympathetic ganglia. Held attempted to show, for the entire vertebrate series, that cells in the ventral nerve-roots play no part in the histogenesis of the sympathetic ganglia. Marcus maintained that the cells observed by Froriep in the ventral nerve-roots were not displaced from the neural tube, but had previously migrated ventralwards from the neural crests. In spite of these and other attempts to prove that the cells entering the sympathetic ganglia, are derived solely from the spinal ganglia and the neural crests, the conclusion of Froriep that cells of medullary origin enter the sympathetic primordia, has been amply confirmed by the work of later investigators.

The majority of the older investigators who studied the development of the autonomic system confined their observations to the sympathetic trunks and prevertebral plexuses. No extensive observations on the development of the autonomic plexuses which are related to the vagi, namely, the pulmonary, cardiac, and enteric plexuses, were published prior to the earlier papers of the present writer in 1909 and 1910 (35–38). It was quite generally assumed, however, that these plexuses have an origin in common with the sympathetic trunks and the prevertebral sympathetic plexuses. Abel's (1) first paper was in full accord with this assumption. According to her conclusions set forth in that paper, the enteric plexuses in the chick arise "from cells which migrate from the spinal cord and the intervertebral ganglia downward through the mesentery to the gut." Abel's later work is mentioned on page 26.

Data bearing on the development of the cranial autonomic ganglia, with the exception of the ciliary ganglion, published prior to 1910 are fragmentary and incomplete. Hoffmann (30), Ewart (14), and Chiarugi (10, 11) supported the theory that the ciliary ganglion arises from cells which advance from the semilunar ganglion into the oculomotor nerve, either directly or by way of the ophthalmic nerve. Dohrn (13) advanced the opinion that in the Elasmobranchii the

ciliary ganglion arises from cells which are displaced from the midbrain along the path of the oculomotor nerve. Béraneck (4), Reuter (58), and Rex (59) described the ciliary ganglion as arising from cells present in the oculomotor nerve, but none of these writers determined the exact sources of these cells. According to Carpenter's (9) observations on embryos of the chick, the primordium of the ciliary ganglion arises from cells which migrate from the midbrain along the oculomotor nerve, but cells which advance from the semilunar ganglion along the ophthalmic nerve also enter this primordium later. In the absence of adequate data bearing on the development of the other autonomic ganglia in the head, it was quite generally assumed that the sphenopalatine, otic, and submaxillary ganglia arise exclusively from cells which become displaced from the semilunar ganglion.

Such in brief was the status of the knowledge of the development of the autonomic nervous system when the present writer initiated a series of studies on its development and its histogenetic relationship to the cerebrospinal nervous system. These studies involved observations on preparations of embryos of types of the several classes of vertebrates, including the human species. The results of the earlier studies in this series (36–44) showed clearly that the autonomic ganglia bear the same histogenetic relationship to the cerebrospinal nervous system in all classes of vertebrates. The ganglia of the sympathetic trunks differ somewhat in their morphogenesis in the several classes, but in all the vertebrate embryos studied, they arise from cells of cerebrospinal origin which are displaced peripherally along the dorsal and ventral roots of the spinal nerves. Some cells of the same origin advance beyond the primordia of the sympathetic trunks and give rise to the prevertebral sympathetic ganglia. The ganglia in the pulmonary, cardiac, and enteric plexuses in the esophagus and stomach are not composed of cells which advance peripherally with those incorporated in the primordia of the ganglia of the sympathetic trunks and prevertebral plexuses, but of cells which are displaced peripherally along the paths of the vagi. The writer's observations on the development of the ciliary ganglion agree in the main with those of Carpenter (9), and indicate that this ganglion arises from cells which advance peripherally along both the oculomotor and ophthalmic nerves. The data bearing on the development of the sphenopalatine, otic, submaxillary, and sublingual ganglia in the higher vertebrates,—data

included in the series of papers referred to above,—were incomplete and in part erroneous. The writer's conclusions regarding the developmental relationships of these ganglia are fully set forth in a later paper (45). The primordium of the sphenopalatine ganglion comprises cells which advance peripherally along the greater superficial petrosal nerve as well as those which are displaced from the semilunar ganglion along the maxillary nerve. The primordium of the otic ganglion arises from cells which advance peripherally along the lesser superficial petrosal nerve. Later on, it also receives cells from the semilunar ganglion. The submaxillary and sublingual ganglia arise mainly from cells of trigeminal origin. These conclusions in part corroborate those of Stewart (61), based on observations of preparations of embryos of the rat. Stewart maintained that the primordium of each cranial autonomic ganglion, with the exception of the ciliary ganglion, arises exclusively from cells advancing peripherally along the nerve which, in the adult, conveys its preganglionic fibers.

The writer's findings regarding the genetic relationship of the pulmonary, cardiac, and enteric plexuses to the vagi and to the sources of the cells which give rise to the ganglia in these plexuses, were corroborated especially by the work of Abel (2) on embryos of the chick and that of Stewart (61) on embryos of the rat. The theory that the ganglia of the sympathetic trunks and prevertebral plexuses originate, at least in part, from the cells of medullary origin which advance peripherally along the ventral spinal nerve-roots, has also been supported by various recent investigators, especially by Ganfini (18-22) who published extensive and detailed observations on the development of the autonomic nervous system in embryos of various types of vertebrates. According to his findings the cells constituting the primordia of the ganglia of the sympathetic trunks, are those which have advanced peripherally along both the dorsal and ventral nerve-roots. The cells then advance farther ventralwards from these primordia and give rise to the prevertebral ganglia. The enteric plexuses, according to Ganfini, start mainly from cells which migrate ventralwards from the primordia of the sympathetic trunks and enter the wall of the digestive tube. He recognized cells which advance peripherally along the vagi and enter the pulmonary, cardiac, and esophageal plexuses, but interpreted them as cells which become displaced from the superior cervical sympathetic ganglia. He recognized the double origin of the ciliary ganglion, but concluded that the sphenopalatine, otic, and submaxil-

lary ganglia are derived from the semilunar ganglion. Rau and Johnson (56) also described the primordia of the sympathetic trunks in embryos of the sparrow as arising in part from cells which become displaced from the neural tube along the paths of the ventral nerve-roots. Uchida (64), who reported extensive observations on the development of the autonomic nervous system in reptiles (Trigonocephalus), birds (chick), and mammals (cat, dog, mouse, pig, calf), also traced cells from both the ventral part of the neural tube and the spinal ganglia into the primordia of the sympathetic trunks. He concluded, on the basis of his findings, that the cardiac, pulmonary, and enteric plexuses in the esophagus and stomach contain mainly cells which are displaced distally along the vagi, but that the enteric ganglia in the intestine arise from cells of sympathetic origin and later also receive cells of vagus origin. Contrary to the findings of nearly all the more recent investigators in this field, E. Müller (51) and Müller and Ingvar (52) vigorously opposed the theory that cells of medullary origin become displaced into the sympathetic primoridia, and supported the older theory according to which the sympathetic ganglia arise exclusively from cells derived from the spinal ganglia or neural crests.

EMBRYOLOGICAL DATA

Sympathetic Trunks

The aggregates of cells constituting the primordia of the ganglia of the sympathetic trunks, first appear in the lower thoracic and upper abdominal regions of human embryos which are about 5 mm. in length. They are situated along the dorsolateral aspects of the aorta. The cells of nerve origin are somewhat scattered and may be differentiated from the mesenchymal cells by the somewhat larger size and more intense staining reaction of their nuclei (Fig. 1). In embryos 6 mm. in length, such aggregates of cells may be observed from the lower cervical to the sacral region. The cells of nerve origin in the sympathetic primordia gradually become more numerous and more closely aggregated. The ganglionic primordia are arranged segmentally, but by reason of the marked curvature of the embryo they lie so close together that the entire series constitutes a continuous column of loosely aggregated cells. This condition continues until the embryos have attained a length of 9 to 10 mm., when the sympathetic primordia are present from the upper cervical to the sacral region. As

development advances, the segmental character of the sympathetic primordia gradually becomes apparent and the cell-aggregates become connected by longitudinal fibers. In the cervical and upper thoracic segments, the sympathetic primordia lie along the dorsolateral aspects of the descending aortae and in close proximity to them. The position of these primordia, seems to be determined at least in part by the position of the paired descending aortae. Inasmuch as these vessels lie at an appreciable distance from the median plane and

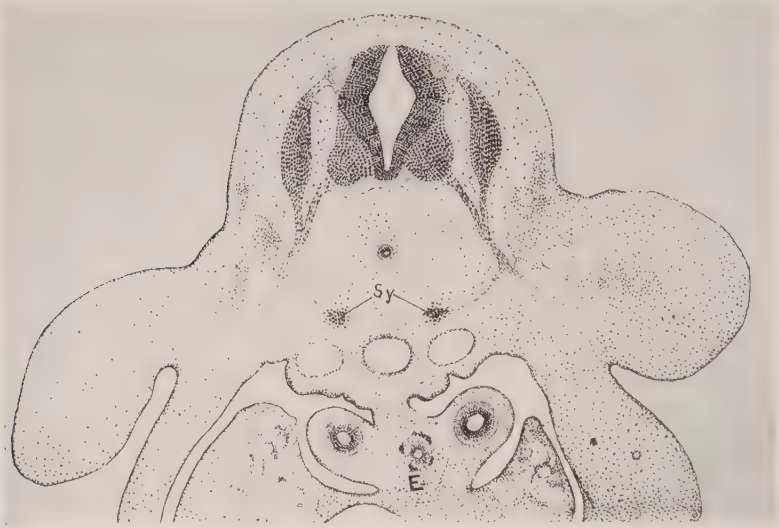


FIG. 1. Transverse section through the thoracic region of a human embryo 7 mm. in length. *E*, esophagus; *Sy*, primordia of sympathetic trunks.

converge toward the unpaired dorsal aorta, the sympathetic trunks lie farther from the median plane in the cervical and upper thoracic than in the lower thoracic and lumbar segments.

In preparations of human embryos 5 or 6 mm. in length in which the primordia of the sympathetic trunks were present only in the lower thoracic and upper lumbar segments, the fibers of the communicating rami could not be traced into these cell-aggregates. In preparations of embryos which are somewhat larger (7 mm. in length), the fibers of the communicating rami extend into the sympathetic primordia throughout the greater part of the thorax and abdomen (Fig. 2). In

the abdominal region, some of these fibers tend ventralwards along the lateral aspects of the aorta. In preparations of embryos which are still farther advanced these fibers extend into the primordia of the prevertebral ganglia lying along the ventrolateral aspects of the aorta (Fig. 3). As early as fibers can be observed in the communicating rami they are accompanied by cells identical with those in the sympathetic primordia. Cells of the same character are also present in the spinal nerve-trunks and in their dorsal and ventral roots. These are

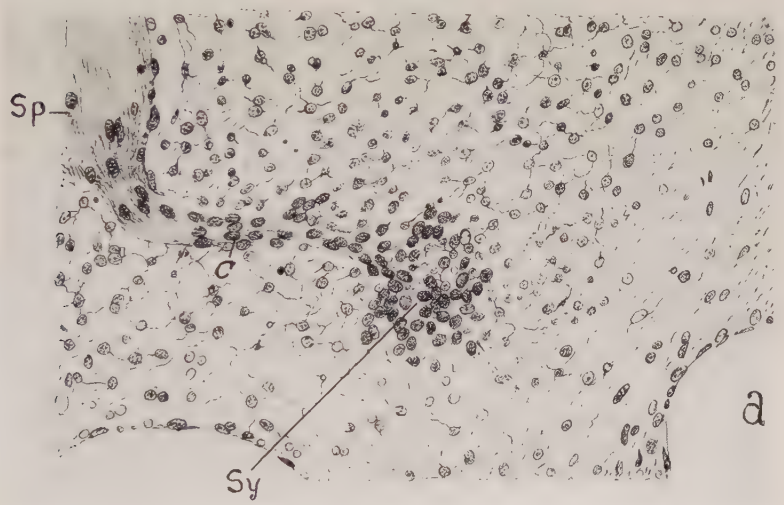


FIG. 2. Area of section shown in Fig. 1, under higher magnification, showing primordium of sympathetic trunk and communicating ramus. *a*, aorta; *c*, communicating ramus; *Sp*, spinal nerve; *Sy*, sympathetic primordium.

cells of cerebrospinal origin which advance peripherally along the paths of the nerves. The majority of the cells which deviate from the nerve-trunks along the paths of the communicating rami, enter the sympathetic primordia. Cells apparently of the same character are present in the ventral nerve-roots both within and without the external limiting membrane. Occasionally an individual cell may be observed partly within and partly without this membrane. Obviously, cells in this position are in the process of emerging from the wall of the neural tube. In preparations of these early embryos, the spinal ganglia are not sharply delimited distally, but cells apparently become

displaced from the distal ends of the spinal ganglia into the dorsal nerve-roots. These cells appear identical with those in the ventral nerve-roots. Consequently, the cells of medullary origin cannot be distinguished from those of ganglionic origin in the spinal nerve distal to the junction of the dorsal and ventral roots. The evidence at hand

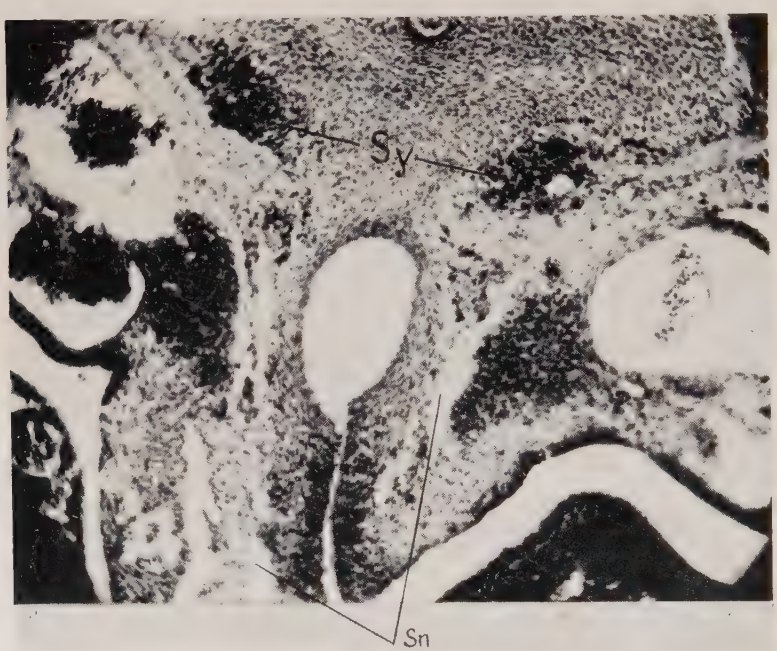


FIG. 3. Transverse section through the upper abdominal region of a human embryo about 12 mm. in length. *Sn*, nerve-fiber tracts growing ventralwards from the primordia of the sympathetic trunks into the primordia of the prevertebral plexuses; *Sy*, primordia of sympathetic trunks.

indicates that cells from both these sources enter the sympathetic primordia.

As stated above, cells of cerebrospinal origin had already reached the sites of the sympathetic primordia, in the smaller embryos studied, before fibers of the communicating rami could be traced in these locations. This is also in accord with the writer's observations on preparations of other vertebrate embryos. Certain other recent

investigators have also expressed the opinion that many of the cells which enter the sympathetic primordia, migrate peripherally in advance of the growing nerve-fibers. Streeter (62) emphasized the early migration of cells into the sympathetic primordia in human embryos. He expressed the opinion that the majority of the cells entering the primordia of the ganglia of the sympathetic trunks, advance toward the aorta before fibers are present in the communicating rami; consequently, he described the communicating rami in early human embryos as cellular strains. Ganfini (21, 22) also described the communicating rami in early mammalian embryos (guinea-pig and pig) as cellular structures. That the distal portions of growing nerve-fibers are not brought out clearly by the ordinary processes of staining, is well known. It may be assumed, therefore, that fibers of the communicating rami extend well into the sympathetic primordia along the aorta somewhat earlier than the recorded data seem to indicate. Nevertheless, the earliest cells probably enter the primordia of the sympathetic trunks somewhat in advance of the growing nerve-fibers.

In embryos of the turtle, many of the cells which enter the primordia of the sympathetic trunks, advance from the spinal nerves, not along the paths of the communicating rami, but directly through the mesenchyme (Kuntz (39-42)). Ganfini (19) also observed the displacement of cells destined to become incorporated in the sympathetic primordia directly through the mesenchyme in embryos of other reptilian types. These observations show clearly that a fibrous tract is not essential for the peripheral displacement of cells of cerebrospinal origin in reptilian embryos. The fact that in mamalian embryos, as in the embryos of lower vertebrates, the cells of nerve origin in the early primordia of the sympathetic ganglia are scattered somewhat widely, also suggests that they may have migrated into these primordia in advance of the growing nerve-fibers. If they could not be displaced in advance of the growing fibers of the communicating rami they would probably be scattered less widely even in the early phases of development.

In preparations of human embryos 9 to 10 mm. in length, cells of cerebrospinal origin are still abundant in the spinal nerve-trunks and communicating rami, indicating that the peripheral migration of these cells is still going on. The cells in the sympathetic primordia are also more numerous and are arranged more compactly than those in the earlier embryos. Mitotic figures in the sympathetic primordia also

indicate that the cells increase in number by local proliferation. Preparations of human embryos 11 or 12 mm. in length, afford little evidence that the migration of cells into the primordia of the sympathetic trunks continues much beyond this stage.

The primordia of the sympathetic trunks arise somewhat later in the cervical region than in the thorax. This fact was noted by all the earlier investigators who made special mention of the development of the cervical portion of the sympathetic trunks in embryos of the higher vertebrates. It was also noted that these primordia gradually extend cephalad from the upper thoracic level as continuous columns of cells until they reach the upper cervical segments. Yet, it was quite generally assumed that even in the higher vertebrates each pair of cervical nerves makes its contribution of cells to the cervical sympathetic ganglia. According to Ganfini (21, 22), cellular communicating rami extend from the cervical spinal nerves, in mammalian (guinea-pig and pig) embryos, toward the primordia of the sympathetic trunks along which "neurocytes" advance into the latter. He maintained that these cellular rami persist for a short time and then disappear, after which there are no connections between the cervical spinal nerves, except the last ones, and the sympathetic trunks until the gray communicating rami arise. The writer was unable to substantiate these observations of Ganfini's, either in embryos of the pig or in human embryos. Nor could he obtain any evidence that cells enter the primordia of the cervical sympathetic ganglia via the cervical spinal nerves. The primordia of the sympathetic trunks advance cephalad from the lower cervical region both by the displacement of cells along the dorsal aspects of the descending aortae and by cell-proliferation. These primordia do not appear segmented in early embryos, but remain continuous cell-columns until their segmentation (which results in the formation of the cervical sympathetic ganglia), takes place.

In human embryos 10 mm. in length, the segmental character of the sympathetic trunks is apparent throughout the greater part of their extent. The aggregates of cells have become larger and more compact, but some cells of nerve origin still remain somewhat scattered and, although the ganglionic masses in adjacent segments are connected by longitudinal fibers, these connecting rami are nowhere free from sympathetic cells. As the curvature of the embryo becomes less marked, with advancing development, the ganglia of the sympathetic trunks become more widely separated. They also become more com-

pact and more sharply delimited. In human embryos 15 mm. in length, the segmental character of the sympathetic trunks is well marked below the cervical region. The segmentation of the cervical portion, which results in the cervical sympathetic ganglia, is also apparent. Fibers may also be traced cephalad from the superior cervical ganglia along the internal carotid arteries. The superior cervical ganglia are not sharply delimited at their upper poles, and some cells apparently advance along the fibers of the internal carotid nerves. In embryos 20 to 22 mm. in length, the ganglia of the symthetic trunks have taken definite form and are sharply delimited, the fibrous rami connecting them with each other are relatively free from sympathetic cells, and the trunks have assumed a definite relationship to the vertebral condensations.

Prevertebral Plexuses

The direct genetic relationship of the prevertebral sympathetic plexuses to the sympathetic trunks is quite generally conceded. The primordia of the ganglia of these plexuses arise along the ventrolateral aspects of the abdominal aorta. In the upper abdominal region of human embryos 6 mm. in length, cells may be traced in small numbers from the primordia of the ganglia of the sympathetic trunks ventralwards along the lateral aspects of the aorta. In embryos which are somewhat farther advanced, the primordia of the ganglia of the sympathetic trunks in this region are not sharply delimited ventrally, but cells apparently become detached from these cell-aggregates and advance ventralwards into the primordia of the prevertebral ganglia. As the fibers of the communicating rami in this region grow into the primordia of the sympathetic trunks, some of them continue through these primordia and tend ventralwards in the direction of the primordia of the prevertebral ganglia. Many of the cells which advance into the latter primordia accompany these fibers; therefore, some of the cells which enter the prevertebral ganglia need not be regarded as being derived from the primordia of the sympathetic trunks. They advance from the spinal nerves along the communicating rami and tend ventralwards along the course of the fibers which enter the prevertebral ganglia without actually becoming incorporated into the primordia of the ganglia of the sympathetic trunks. In embryos which are still farther advanced, fibers may also be traced from the primordia of the thoracic sympathetic ganglia below the

fourth or fifth thoracic segment toward the primordia of the prevertebral ganglia in the upper abdominal region. These are mainly fibers which join the sympathetic trunks through the communicating rami of the thoracic nerves and, continuing toward the prevertebral plexuses, give rise to the splanchnic nerves. In human embryos 10 mm. and over in length, the aggregates of cells which constitute the primordia of the prevertebral ganglia, are conspicuous along the abdominal aorta. Some cells have already become displaced laterally from these cell-masses, toward the primordia of the adrenal glands and along the renal arteries. The greatest accumulation of sympathetic cells ventral to the abdominal aorta, occurs at the origin of the celiac artery. The several prevertebral plexuses are not yet clearly delimited. Neither can fibers be traced from these plexuses into the mesentery. As development advances, the various prevertebral plexuses become more clearly delimited and the ganglionic cell-aggregates become more compact. Cells may be traced from these ganglia into the adrenal bodies and along the renal and spermatic (or ovarian) arteries.

Plexuses Related to the Vagus Nerves

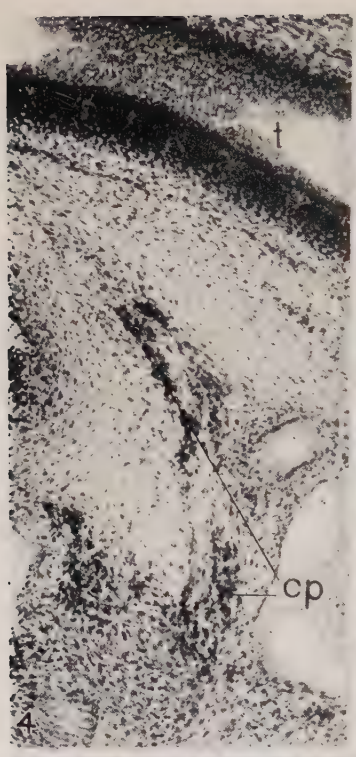
The plexuses related to the vagi, namely, the pulmonary, cardiac, and enteric plexuses, particularly in the esophagus and stomach, arise from cells of cerebrospinal origin which advance peripherally along the paths of the vagi. This was first determined in mammalian (pig) embryos (Kuntz (35, 36)) and later in embryos of types of the other classes of vertebrates. Abel (2), who had previously (1) maintained that the enteric plexuses in the chick are derived exclusively from cells which migrate from the neural tube and spinal ganglia, re-investigated the development of these plexuses and confirmed the writer's findings. She also corroborated the writer's findings regarding the developmental relationship of the pulmonary and cardiac plexuses to the vagi. Stewart (61), whose studies were based on embryos of the rat, concluded that part if not all of the nerve-cells in the pulmonary, cardiac, and enteric plexuses, including the ganglia in the upper part of the intestine, are of vagus origin.

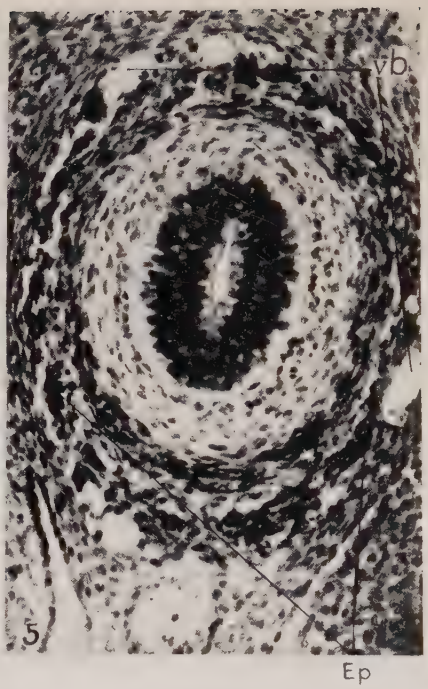
In human embryos 5 mm. in length, the vagus nerves may be traced distally somewhat beyond the bifurcation of the trachea. Like the spinal nerves, they contain cells of cerebrospinal origin. In favorable sections through the vagus roots, continuous lines of cells of medullary

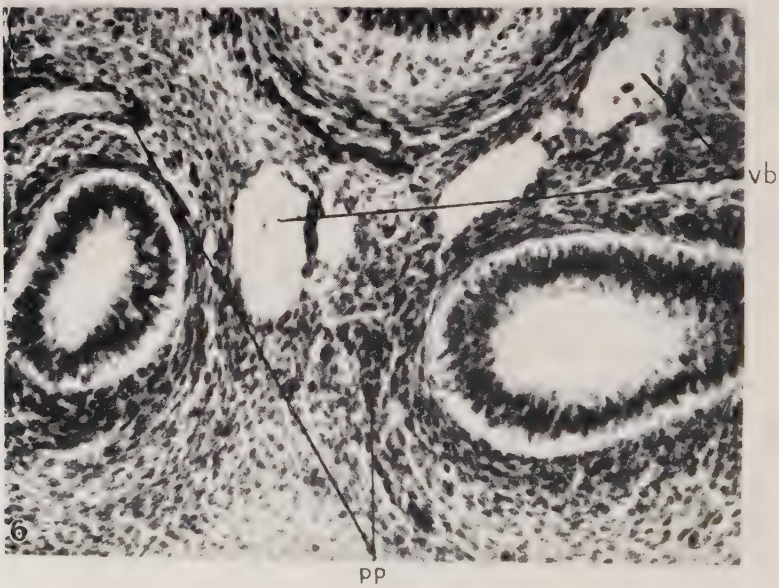
origin may be observed extending into these roots, indicating an active migratory process. In sagittal sections, the ganglia on the vagus trunk do not appear to be sharply delimited distally, but lines of cells extend from the distal ganglion into the nerve-trunk. Furthermore, cells identical in appearance with those in the ganglionic cell-masses are present in abundance in the vagus nerve as far as the latter can be traced. These cells are also identical in appearance with those which advance from the neural tube and spinal ganglia along the spinal nerves. Vagus branches bearing small aggregates of such cells may already be traced toward the esophageal wall.

In embryos 6 mm. in length, vagus branches may be traced to the stomach and for a short distance along its lesser curvature, toward the roots of the lungs, and toward the bulbar region of the heart. All these branches contain many cells of nerve origin. In embryos 7 to 9 mm. in length, the pulmonary branches have reached the roots of the lungs and the cardiac branches may be traced close to the base of the heart. As observed in sagittal sections of an embryo 9 mm. in length, the cardiac branches of the vagus nerve are accompanied by numerous cells of nerve origin which tend to become aggregated near their growing tips. In an embryo 14 mm. in length, these branches bear relatively large aggregates of such cells near their distal ends (Fig. 4). These cell-masses constitute the primordia of the cardiac plexus. Over the dorsal aspect of the heart the esophageal plexus, which is already well formed, comes into close proximity to the walls of the atria. Vagus branches, with their accompanying cell-aggregates, form a plexiform meshwork around the lower portion of the esophagus, which is somewhat more abundant over the dorsal and lateral aspects of the esophagus than between the esophagus and trachea (Fig. 5). Below the bifurcation of the trachea, vagus branches containing cells of nerve origin, may be traced into the roots of the lungs where masses of nerve-cells occur in proximity to the bronchi and pulmonary vessels (Fig. 6). These nerve-complexes, constituting the primordia of the pulmonary plexuses, are continuous with the esophageal plexus and with that portion of the cardiac plexus associated with the walls of the atria.

The esophageal plexus is well formed before cells of nerve origin can be found in the esophageal wall. In human embryos 7 to 9 mm. in length, numerous nerve-elements have advanced into the wall of the esophagus, but a definite concentric arrangement of these cells is not







FIGS. 4-6.

yet apparent. In embryos 10 mm. in length, vagus branches accompanied by migrant nerve-cells may be traced along the wall of the stomach. Many of these cells penetrate the stomach wall with the terminal vagus branches and become incorporated into the primordia of the enteric plexuses. As development advances, the primordia of the enteric plexuses also become apparent in the intestine. The cells of nerve origin in the wall of the digestive tube gradually become more numerous and, as the muscular and submucous layers become differentiated, the nerve-elements become aggregated in minute ganglionic masses which assume a concentric arrangement in two layers constituting the primordia of the myenteric and submucous plexuses.

It is significant that no paths along which cells advance from the sympathetic trunks or prevertebral plexuses into the pulmonary, cardiac, and enteric plexuses in the more proximal portions of the digestive tube are established during the early stages of development. Indeed, the early development of the latter plexuses goes on simultaneously with that of the sympathetic trunks and prevertebral plexuses. Sympathetic nerves grow into the plexuses related to the vagi later, but not until the great majority of the cells which enter their primordia are already present. The possibility that some cells may enter these plexuses via the sympathetic nerves which join them is not precluded.

According to Uchida (64), who corroborated the writer's findings regarding the genetic relationship of the enteric plexuses in the esophagus and stomach to the vagi, cells become displaced from the sympathetic primordia into the walls of the intestine before cells of vagus origin have advanced far enough to reach the intestine. He concluded, on the basis of his findings, that the primordia of the enteric ganglia in the intestine arise mainly from cells of sympathetic origin,

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Fig. 4. (Upper left.) Sagittal section of a human embryo 14 mm. in length, showing trachea and upper portion of heart. *Cp*, portion of cardiac plexus; *t*, trachea.

Fig. 5. (Upper right.) Transverse section of the esophagus in the upper thoracic region of a human embryo 10.1 mm. in length. *Ep*, cell-masses in esophageal plexus; *vb*, vagus branches.

Fig. 6. (Lower centre.) Transverse section at the level of the roots of the lungs in a human embryo 10.1 mm. in length. *pp*, primordia of the pulmonary plexus; *vb*, vagus branches.

and later also receive cells of vagus origin. Van Campenhout (7) also claims to have obtained evidence of the early displacement of cells from the sympathetic primordia into the walls of the intestine. He concluded, on the basis of his findings, that the enteric plexuses include mainly cells of vagus origin throughout the esophagus and stomach, but are made up mainly of cells of sympathetic origin in the intestine.

These findings of Uchida's and van Campenhout's regarding the origin of the enteric plexuses in the intestine differ somewhat from the author's results, although the latter do not preclude a contribution of cells of sympathetic origin to these plexuses in any part of the intestine, and strongly suggest such a contribution in its more distal parts. Yet, the similarity in the functional relationships of the enteric plexuses in the stomach and small intestine to the vagi favors the assumption that they sustain a similar genetic relationship to the vagi in both these divisions of the digestive tube. The enteric plexuses in the hind-gut probably sustain a developmental relationship to the sacral nerves corresponding to that which the plexuses in the proximal parts of the digestive tube bear to the vagi. Exact data concerning the rôle of the sacral nerves in the development of the enteric plexuses are not available. More exact knowledge regarding the developmental relationships of the enteric plexuses throughout the small and large intestine, awaits the results of further investigation.

Cranial Autonomic Ganglia

Ciliary ganglion. According to the majority of the more recent investigators, the ciliary ganglion arises from cells which advance peripherally both along the oculomotor and ophthalmic nerves. Broman (5) and Streeter (62) described the ciliary ganglion in human embryos as arising from cells derived exclusively from the semilunar ganglion. According to Ganfini (21), the contribution of cells from the oculomotor nerve to the ciliary ganglion, is less obvious in mammalian embryos than in the embryos of other vertebrates; however, inasmuch as it has been clearly shown that the ciliary ganglion arises in part from cells which advance peripherally along the oculomotor nerve in other classes of vertebrates, he concluded that this ganglion is genetically related to both the oculomotor and ophthalmic nerves also in mammals. Stewart (61) found no evidence, in embryos of the

rat, that any cells which become incorporated in the ciliary ganglion advance peripherally along the oculomotor nerve, although he maintained that all the other cranial autonomic ganglia arise exclusively from cells which advance into their primordia along the nerves conveying the preganglionic fibers to each ganglion, respectively.

In early human embryos, the migration of cells along the oculomotor nerve is not very apparent; however, some cells apparently of nerve origin occur in the nerve-trunk. In some embryos an aggregate of intensely staining cells was observed on the oculomotor nerve-trunk at the level at which the ciliary ganglion arises, before cells could be traced into this location from the ophthalmic nerve. The ophthalmic nerve has the appearance, in early human embryos, of a path along which cells are being displaced peripherally. Continuous lines of cells identical with those in the semilunar ganglion extend from this ganglion along the nerve-trunk. Cells also become aggregated very early in the course of the ophthalmic nerve at a point just proximal to the origin of the nasociliary ramus. As this aggregate of cells increases in size it advances toward the oculomotor nerve until it becomes continuous with the aggregate of cells already present on the latter nerve. The primordium of the ciliary ganglion now consists of a continuous mass of cells extending from the ophthalmic to the oculomotor nerve. At this stage (14 mm.) nerve-fibers may be traced from the oculomotor nerve into the primordium of the ciliary ganglion, but they are largely obscured by the dense aggregate of cells. In embryos somewhat farther advanced this ganglionic mass appears removed somewhat from the ophthalmic nerve-trunk, but it remains in intimate contact with the oculomotor nerve. This intimate relationship to the oculomotor nerve is maintained until relatively late. The mass of cells which constitutes the primordium of the ciliary ganglion in human embryos 14 to 16 mm. in length is relatively enormous, but the great majority of these cells are derived from the semilunar ganglion. Although the aggregate of cells which advance into the ciliary primordium along the oculomotor nerve, is small in comparison with the mass derived from the semilunar ganglion, it is not insignificant. The data at hand warrant the conclusion that in human embryos, as in the embryos of other vertebrates, the ciliary ganglion is genetically related to both the ophthalmic and oculomotor nerves.

Sphenopalatine ganglion. The primoridum of the sphenopalatine ganglion first appears in human embryos about 11 mm. in length. It

arises as an aggregate of cells at the growing tip of the greater superficial petrosal nerve. The cells contained in it apparently have advanced peripherally along this nerve. The geniculate ganglion, from which the greater superficial petrosal nerve arises, is not sharply delimited during early development. Cells apparently become separated from it and advance along the path of the greater superficial petrosal nerve. Cells of nerve origin are present throughout the length of this nerve; consequently, it presents, during the early stages of development, the appearance of a slender nerve-trunk along which cells of nerve origin advance peripherally. It need not be assumed that all these cells have their origin in the geniculate ganglion. Probably, many of them are of medullary origin.

The primordium of the sphenopalatine ganglion lies medial to the maxillary nerve but not in contact with it. The maxillary nerve, in early human embryos, is composed of numerous loosely aggregated bundles of fibers accompanied by numerous cells which apparently are derived from the semilunar ganglion. In embryos 12 to 15 mm. in length, rami may be traced from the maxillary nerve near its origin from the semilunar ganglion into the primordium of the sphenopalatine ganglion. Cells of semilunar origin advance along these rami and mingle with the cells already present in the sphenopalatine primordium. In embryos 20 mm. in length, the rami of the maxillary nerve which join the sphenopalatine ganglion, still contain numerous cells of nerve origin, but the greater superficial petrosal nerve and the nerve in the pterygoid canal are relatively free from such cells. Apparently, migration of cells into the sphenopalatine ganglion continues farther along the maxillary rami than along the greater superficial petrosal nerve. In embryos 20 mm. and over in length, some of the cells in the maxillary rami may already be recognized as neuroblasts. This may be regarded as evidence that at least some of the cells entering the sphenopalatine ganglion via the maxillary rami, actually become differentiated into neurones. It is significant, however, that the cells which enter the sphenopalatine primordium earliest, advance along the course of the nerve which conveys its preganglionic fibers. The union of the deep petrosal and the greater superficial petrosal nerves takes place before the migration of cells along the latter nerve ceases, but there is no conclusive evidence that cells enter the sphenopalatine ganglion via the deep petrosal nerve. (Fig. 7.)

The foregoing observations warrant the conclusion that the sphenopalatine ganglion arises, in human embryos, in part from cells of cerebrospinal origin which advance peripherally along the greater superficial petrosal nerve, and in part from cells which advance from the

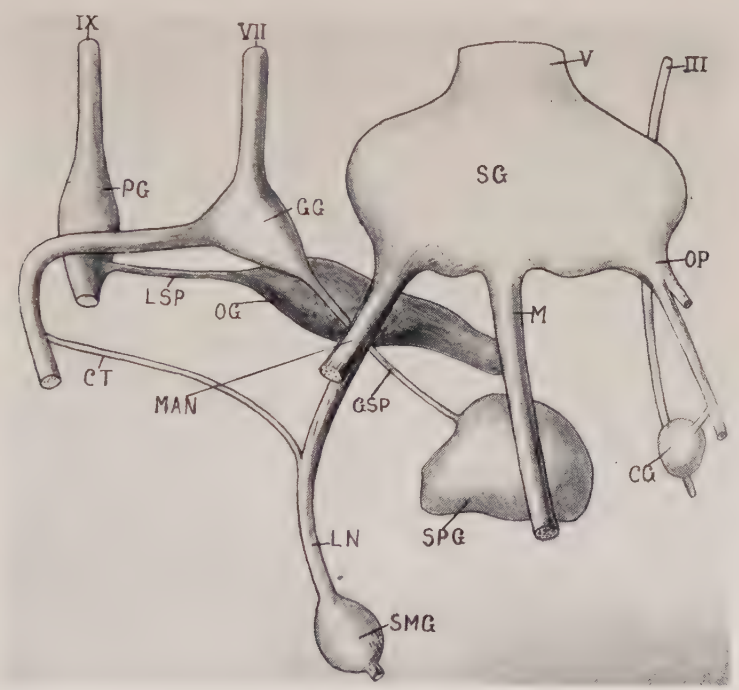

FIG. 7. Diagrammatic reconstruction of the larger cranial autonomic ganglia and the nerves to which they are histogenetically related, in a human embryo about 20 mm. in length. *CG*, ciliary ganglion; *CT*, chorda tympani; *GG*, geniculate ganglion; *GSP*, greater superficial petrosal nerve; *LN*, lingual nerve; *LSP*, lesser superficial petrosal nerve; *M*, maxillary nerve; *MAN*, mandibular nerve; *OG*, otic ganglion; *OP*, ophthalmic nerve; *PG*, petrosal ganglion; *SG*, semilunar ganglion; *SMG*, submaxillary ganglion; *SPG*, sphenopalatine ganglion.

semilunar ganglion along the maxillary nerve and its rami. The contribution of cells from the latter source is probably greater than that from the former. Ganfini (21), who studied the development of this ganglion in embryos of the pig and guinea-pig, did not regard the cells which advance along the greater superficial petrosal nerve as suffi-

ciently numerous to play a significant rôle in its development. On the other hand, Stewart (61) maintained, on the basis of observations on embryos of the pig and rat, that the sphenopalatine ganglion arises solely from cells which advance peripherally along the greater superficial petrosal nerve.

Otic ganglion. The primordium of the otic ganglion first appears, in human embryos 9 or 10 mm. in length, as an aggregate of cells at the growing tip of the lesser superficial petrosal nerve. In embryos 7 to 8 mm. in length, the tympanic branch of the glossopharyngeal nerve extends along the dorsal aspect of the pharynx. Cells apparently become displaced from the petrosal ganglion of the glossopharyngeal nerve into this ramus and advance along its course. In sagittal sections of embryos 8 mm. in length, this ramus may be traced to the level of the geniculate ganglion. No marked accumulations of cells occur along its course, but its fibers are accompanied by numerous cells of nerve origin, giving it the appearance of an early migration path. When an accumulation of cells at its growing tip may first be recognized it has reached a point a little below the lower level of the semilunar ganglion. The primordium of the otic ganglion increases in size rapidly and assumes an elongated form. Its upper extremity soon extends above the lower level of the semilunar ganglion and lies in close proximity to this ganglion and the proximal portion of the mandibular nerve, but during the early phases of its development there is no apparent connection between the otic primordium and the semilunar ganglion. In embryos 13 mm. and over in length, it is apparent that cells of semilunar origin become incorporated in the primordium of the otic ganglion. The otic ganglion now lies in immediate contact with the proximal portion of the mandibular nerve. This nerve, like the other divisions of the trigeminal, contains numerous cells of cerebrospinal origin, some of which deviate from its course along the slender rami which join the otic ganglion. Inasmuch as the mandibular nerve has a motor as well as a sensory root, it is not improbable that a portion of the cells which advance peripherally along its course are derived directly from the hind-brain, but it is quite apparent that many of the cells of trigeminal origin which enter the otic ganglion are derived directly from the semilunar ganglion. In embryos 18 to 20 mm. in length, the rami of the mandibular nerve leading into the otic ganglion, still contain cells of nerve origin. The displacement of cells into the otic ganglion along these rami has not as

yet ceased entirely. On the other hand, the lesser superficial petrosal nerve is relatively free from cells of this type in embryos which are still less advanced in their development. As in the case of the sphenopalatine ganglion, the displacement of cells into the otic ganglion continues later along the rami which connect it with the trigeminal nerve than along the nerve which conveys its preganglionic fibers. While the earliest cells which enter the otic primordium advance along the latter nerve, the majority of the cells entering this primordium later are of trigeminal origin. Broman (5) and Streeter (62), who studied the development of the otic ganglion in human embryos, and Ganfini (21), who used embryos of the pig and guinea-pig, supported the theory that the cells giving rise to this ganglion, are derived exclusively from the semilunar ganglion. On the contrary, Stewart (61) in studying preparations of embryos of the pig and rat, maintained that the otic ganglion arises solely from cells which are displaced distally along the lesser superficial petrosal nerve.

Submaxillary ganglion. The primordium of the submaxillary ganglion first appears in human embryos 10 to 11 mm. in length, as an accumulation of cells in the path of the lingual division of the mandibular nerve. In view of the developmental relationship of the other cranial autonomic ganglia to the nerves which convey their preganglionic fibers, one would expect to find cells of facial origin displaced into the primordium of the submaxillary ganglion along the chorda tympani. The chorda tympani, however, does not join the lingual nerve until the primordium of the submaxillary ganglion has attained considerable size. It is quite probable that cells which advance from the facial nerve along the chorda tympani, enter the primordium of the submaxillary ganglion during its later development, i.e., after the junction of the chorda tympani with the lingual nerve is effected; but the cells which enter this primordium early, are cells of trigeminal origin, some of which probably advance directly from the hind-brain along the motor root of the mandibular nerve. The migration of cells along the lingual nerve also continues until there is no longer any evidence of cell-migration along the chorda tympani. Obviously, the great majority of the cells entering the submaxillary ganglion, are of trigeminal origin. This conclusion is in full accord with that of Broman (5) and Streeter (62) regarding the sources of the cells which enter the primordium of the submaxillary ganglion. Ganfini (21) advanced the opinion that the submaxillary ganglion arises solely from

cells of trigeminal origin. On the other hand, Stewart (61) concluded that the submaxillary ganglion arises exclusively from cells which advance peripherally along the chorda tympani, although he admitted that by reason of the intimate relationship of the primordium of this ganglion with the lingual nerve, direct observations lend little support to this conclusion.

Sublingual and lingual ganglia. The primordium of the sublingual ganglion arises as an accumulation of cells in the path of the lingual nerve, somewhat distal to the primordium of the submaxillary ganglion. Cells of nerve origin also advance along the branches of the lingual nerve and give rise to small ganglionic masses in the tongue. These minute ganglia remain associated with the branches of the lingual nerve. Obviously the cells which give rise to the sublingual ganglion and the smaller ganglia in the tongue associated with the branches of the lingual nerve are derived from the same sources as those which give rise to the submaxillary ganglion.

Minute ganglia also occur in the posterior portion of the tongue. These ganglia are associated with the lingual ramus of the glossopharyngeal nerve. As this nerve continues into the tongue, groups of cells accumulate near its growing extremity. Some of these cell-groups remain closely associated with the nerve-trunk. Other cells advance along its terminal branches and give rise to minute ganglia throughout the portion of the tongue which is innervated by the glossopharyngeal nerve. These ganglia arise exclusively from cells which advance peripherally along the glossopharyngeal nerve.

Histogenetic Relationships

The conception that the cells which give rise to the ganglia of the sympathetic trunks and prevertebral plexuses are derived at least in part from the neural tube via the ventral roots of the spinal nerves, represents a wide departure from the older theory according to which the cells which enter the sympathetic primordia are derived exclusively from the spinal ganglia or neural crests. It is in full accord, however, with the present knowledge of the functional relationships of the sympathetic system. That the neurones in the ganglia of the sympathetic trunks and prevertebral plexuses are essentially efferent in function is quite generally conceded. In view of the fact that within the central nervous system efferent neurones arise mainly in the ventral or basal plate and afferent neurones mainly in the dorsal or alar plate of the

neural tube, it is more logical to assume that the sympathetic neurones are derived from the ventral portion of the neural tube, which is a source of efferent neurones, than from the spinal or neural crest, which

FIG. 8. Drawing from a section of an embryo of Squalus acanthias, showing lines of cells extending from the mantle-layer of the neural tube into the ventral nerve-root (*VN*).

is essentially a source of afferent neurones. Yet, certain recent investigators, especially E. Müller and Ingvar (52), have maintained, even on the basis of experimental embryological studies, that the sympathetic primordia are composed of cells derived exclusively from the spinal

ganglia or neural crests. They contended that no cells of medullary origin become dispaced into the ventral roots of the spinal nerves.

Cells of medullary origin have been observed in the ventral spinal nerve-roots in embryos of all classes of vertebrates. The evidence that these cells are displaced from the ventral part of the neural tube is especially clear in elasmobranch embryos. As early as 1877, Balfour (3) described the early ventral nerve-root in these embryos as "an elongated cellular structure with a wide attachment to the spinal cord." His illustrations indicate the continuity of this cellular structure with the mantle-layer in the wall of the neural tube. Such con-

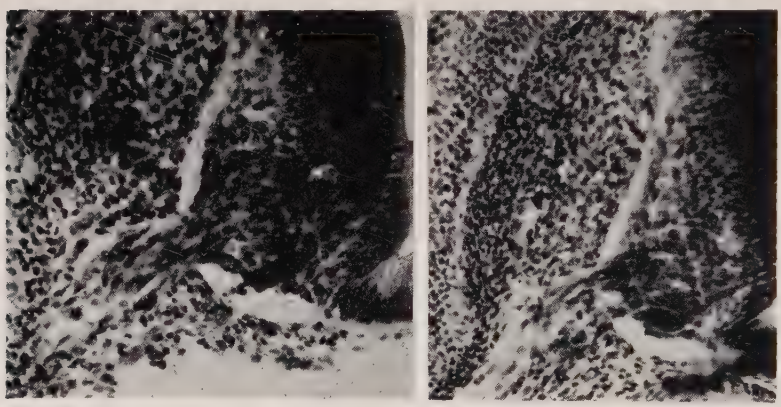

Fig. 9. Photomicrographs of sections of a chick embryo, showing lines of cells extending from the mantle-layer of the neural tube into a ventral nerve-root.

tinuity is also apparent in Figure 8. In preparations of embryos of birds and mammals actual continuity of lines of cells extending from the mantle-layer of the neural tube into the ventral nerve-roots is observed only rarely. This condition, as observed in preparations of an embryo of the chick, is illustrated in Figure 9. Individual nuclei partly within and partly without the external limiting membrane in the ventral nerve-roots occur not uncommonly in preparations of embryos of all the higher vertebrates, including the human species.

In an effort to determine more exactly the rôle of cells of medullary origin in the development of the sympathetic ganglia, embryos of the chick were subjected to an operative procedure, before the close of the second day of incubation, by which a part or all of the nerve-tissue

was destroyed throughout a series of segments. The embryos were allowed to develop until about the close of the fifth day of incubation, when they were killed and prepared for study (Kuntz (46–48)).

Preparations of these embryos showed destruction of varying amounts of nerve-tissue. In some embryos, the spinal ganglia and dorsal nerve-roots were absent on one or both sides throughout a series of segments, while the ventral portion of the neural tube remained intact and the ventral nerve-roots were aparently of normal size. In other embryos only a small ventral portion of the neural tube remained intact in the segments involved. In nearly all these cases ventral nerve-roots were present, but diminished in size in proportion to the degree of destruction of the ventral half of the neural tube. Visceral rami were present wherever a part or all of the portion of the mantle-layer which gives rise to the intermediolateral cell-column, remained intact, but absent wherever this portion of the mantle-layer was completely destroyed and there was no visceral ramus. In still other embryos all the nerve-tissue was destroyed throughout a series of segments. No traces of spinal nerves were observed in these segments.

In every instance in which a ventral nerve-root with a visceral ramus was present, an aggregate of cells representing the sympathetic primordium was also present, even though no traces of a spinal ganglion or dorsal nerve-root could be found; but no sympathetic primordium was observed in any segment in which there was no visceral ramus, even though a small ventral nerve-root was present, except in one instance in which very small sympathetic primordia appeared in the upper thoracic segments in the complete absence of spinal ganglia and neural tube in these segments. Obviously, in this instance, some cells were displaced peripherally in the segments in question before the embryo was subjected to operation. No sympathetic primordia could be found in the lower thoracic segments in the same embryo. Apparently the peripheral displacement of cells of nerve origin is initiated earlier in the upper than in the lower thoracic segments. The majority of the preparations used showed no evidence of the peripheral displacement of cells of neural crest origin before the operative procedure was carried out.

CONCLUSIONS

The experimental data at hand seem to warrant the conclusion that in the absence of spinal ganglion or neural crest cells the primordia of

the ganglia of the sympathetic trunk may arise from cells derived exclusively from the ventral part of the neural tube via the ventral spinal nerve-roots. The fact that such primordia fail to arise in segments in which the portion of the mantle-layer giving rise to the intermediolateral cell-column is destroyed, even though a small ventral nerve-root is present, suggests that the cells which under normal conditions enter the sympathetic primordia via the ventral nerve-roots, are derived mainly from this portion of the neural tube.

That cells which become displaced from the spinal ganglia, enter the sympathetic primordia, under normal conditions, cannot be doubted. Neither can the ultimate fate of the cells of medullary and ganglionic origin, respectively, in the sympathetic primordia be determined by the microscopic study of embryonic material. Certain investigators, particularly Froriep (15) and Cajal (6), advanced the opinion that the sympathetic neurones are derived mainly from cells of medullary origin which enter the sympathetic primordia via the ventral nerve-roots. Froriep was influenced in his opinion by the fact that he regarded the sympathetic neurones as mainly efferent and that the ventral part of the neural tube is essentially a source of efferent neurones. Inasmuch as many of the cells of nerve origin which advance peripherally become differentiated into neurilemma cells, the cells of spinal ganglion origin which become incorporated into the sympathetic primordia could readily be accounted for without assuming that they become differentiated into sympathetic neurones. The data available at present, however, do not warrant the conclusion that no cells of spinal ganglion origin become differentiated into sympathetic neurones. Precisely what part cells derived from the neural tube play in the development of the sympathetic nervous system must still be regarded as an open question.

That the primordia of certain of the cranial autonomic ganglia and the plexuses related to the vagi include cells of both medullary and neural crest origin is less apparent. The cells which migrate from the wall of the hind-brain into the rootlets of the glossopharyngeal nerve, cannot be traced with certainty beyond the petrosal ganglion along the lesser superficial petrosal nerve. Neither can cells of medullary origin in the rootlets of the facial nerve be traced beyond the geniculate ganglion along the greater superficial petrosal nerve. Nor can the cells which migrate from the wall of the hind-brain into the vagus rootlets be traced beyond the ganglia on the vagus trunk. On the other hand,

the presence of one or more ganglia on a nerve-trunk does not preclude the possibility that cells of medullary origin may advance along the nerve, distal to the ganglia. Consequently, cells derived from the wall of the hind-brain may advance along the lesser superficial petrosal and greater superficial petrosal nerves, respectively, into the otic and sphenopalatine ganglia and along the vagus nerves into the pulmonary, cardiac, and enteric plexuses. That the primordium of the ciliary ganglion comprises both cells of medullary and ganglionic origin is evident. Inasmuch as it must be admitted that cells of medullary origin enter the primordia of parts of the autonomic nervous system, there is no reason to assume that any part of the system is derived exclusively from cells of neural crest origin.

DISCUSSION

The following questions submitted to Dr. Kuntz before the Commission, together with the answers to them, are here reported verbatim.

Dr. Tilney: Dr. Kuntz, considering the several varieties of migrations in the formation of the autonomic system such as you have described or indicated, for example:

(*a*) In the ventral root (basal plate),
(*b*) In dorsal root ganglion,
(*c*) In the formation of cellular structures of the communicating rami,
(*d*) In the cephalad extensions to form the cervical cell-column,
(*e*) In the formation of the gray rami,—

do you find any general corroboration of the principles of neurobiotaxis?

Dr. Kuntz: As I understand the principle of neurobiotaxis, it implies that the cells move toward the source of their stimulation. I do not know exactly what to say about the source of stimulation of sympathetic cells in general. Since we regard the sympathetic cells as motor, their stimulus must come through the preganglionic fibers; and I do not see just how we are going to explain the movement of these cells outward from the central nervous system according to any principle such as that of neurobiotaxis.

Dr. Tilney: Is it your opinion that the important neuromuscular mechanism regulated through the ciliary ganglion may determine the participation of a somatic motor nerve in the formation of this ganglion, whereas the other accessory ganglia connected with the cranial nerves are apparently dependent solely upon neural crest derivatives because their innervation is largely glandulo-effector or vascular?

Dr. Kuntz: I am not sure there is a real difference. It appears that the number of cells that move out along the ophthalmic nerve into the ciliary ganglion, is

enormous. That is quite evident. And it is not evident that a great number of cells move out into this ganglion from the neural tube.

But I think one must get the impression from studying embryos that there are more cells in the primordium of the ciliary ganglion than are necessary to account for the number of neurones there in the mature condition. A great number of those cells are going to be used in some other way and if you can assume that any considerable number of cells that get into that primordium are going to be consumed in the formation of neurilemma and other supporting structures, it seems to me it is not material just how many cells there are in the primordium to begin with.

Then, too, you can observe mytotic divisions in those early primordia, so there is some proliferation of these cells even after they have moved out from the central nervous system. I am not sure that there is any real difference in the ciliary and other cranial ganglia.

Dr. Tilney: Even accepting Müller and Ingvar's (52) contention that the sympathetic primordia are derived exclusively from spinal ganglia or neural crest elements, is this interpretation in any way inconsistent with the recognized efferent character of neural elements in the sympathetic system?

Dr. Kuntz: Yes, Müller and Ingvar did maintain that to the end, and even on the basis of some operative material that they used. It seems to me, from my own material and from the sections that I have shown, the evidence is clear that cells move out into the motor roots in such numbers that there is no question but that cells from motor sources enter the sympathetic primordia.

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CHAPTER III

DIVISIONS OF THE VEGETATIVE NERVOUS SYSTEM WITH ITS GANGLIA AND PLEXUSES; PERIPHERAL DISTRIBUTION OF THE VARIOUS PARTS OF THE VEGETATIVE NERVOUS SYSTEM[1]

ANGUS MACDONALD FRANTZ, M.D.

INTRODUCTION[2]

THE vegetative nervous system is that division of the nervous system which supplies with efferent and afferent fibers all the smooth muscle and glandular epithelium of the body. In addition it supplies the heart and probably sends a contribution to the innervation of the so-called voluntary or striated muscles, but this contribution is certainly of less importance than that of the cerebrospinal system. While the activities of the vegetative system are not under the control of the will, they may be profoundly modified by changes which occur in the central system. The fact of this "central representation" is undoubted and the topographical and functional relations which exist with the parent system are taken up in detail elsewhere.

Certain characteristics of the vegetative nervous system stand out prominently. In the first place, the anatomical arrangement of the afferent supply of the viscera is not basically different from that which obtains in the case of the skin, etc. The cell-body of the afferent neurone lies in a dorsal root ganglion or its cranial homologue. Its peripheral process runs distally to the structure innervated and its proximal process enters the neuraxis. The situation is different in the case of the efferent fibers. Apparently without exception, the efferent pathway from neuraxis to viscus is composed of two, and only two, neurones. The cell-body of the second neurone lies outside the central system and there is a tendency for these cell-bodies to be grouped together in structures called ganglia. In consequence of this

[1] From the Neurological Institute, New York.

[2] In the preparation of this article the standard text-books of anatomy, particularly those of Piersol and of Spalteholz, have been consulted freely.

terminology the fibers entering a ganglion, derived from cell-bodies lying in the central system, are called preganglionic. Fibers whose cell-bodies lie in and constitute a ganglion are termed postganglionic. The ganglion is the point where the impulse is transferred, via a synapse, from the preganglionic to the postganglionic system. One preganglionic fiber probably enters into synaptic union with several cells and this anatomical arrangement helps to explain the diffuseness of many reactions in the domain of the vegetative system.

The second peculiarity of the vegetative nervous system is the tendency of its peripheral branches to form plexuses. The peripheral fibers of the cerebrospinal system are usually aggregated into comparatively large nerve-trunks which run directly to their destination with a minimum degree of branching. The fibers of the vegetative system are carried to the viscera to a great extent by means of the blood-vessels, which are thus innervated and which in turn act as supporting and distributing structures. In most cases the vegetative fibers, instead of being collected in a single trunk, form an intricate network, or a plexus, around the arteries and these plexuses usually receive their name from the arteries which carry them.

Two great divisions of the vegetative nervous system are conventionally recognized—divisions which differ from each other in their physiological activities, response to certain drugs, and in their anatomical characteristics. The first of these is the sympathetic system; the second is known as the parasympathetic system.

THE SYMPATHETIC SYSTEM

The cell-bodies of the preganglionic fibers of this system form a column of cells in the lateral horn of the gray matter of the spinal cord from the eighth cervical or first thoracic segment to the third lumbar segment. Fibers make their exit from the cord in company with the somatic fibers of the ventral roots and then, leaving the ventral root, turn forward and enter a ganglion. A nerve-trunk composed of such fibers is called a white ramus communicans. The ganglia which receive the fibers of the white rami communicantes lie for the most part in close proximity to cerebrospinal nerves. In addition to other branches, which will be described later, these ganglia send fibers to each spinal nerve for the innervation of all visceral structures situated in the domain of that nerve. Such a

branch is termed, owing to the lack of myelin sheaths over its fibers, a gray ramus communicans.

There are two orders of ganglia of the sympathetic system. To the first of these belong the vertebral or lateral ganglia, since they lie beside the bodies of the vertebrae from the base of the skull to the coccyx. To the second belong the prevertebral, or collateral, or sometimes plexus ganglia. They lie more in the midline, in the abdominal cavity, in close association with the plexuses to be described later.

The lateral ganglia of the sympathetic system are connected with each other by a continuous nerve-trunk composed of pre- and postganglionic fibers. This trunk with its associated ganglia is called the ganglionated cord and is divided for descriptive purposes into cervical, thoracic, lumbar and sacral divisions.

I. The Cervical Division

This division consists of three ganglia: the superior, middle and inferior cervical ganglia, connected by an association cord, the whole structure lying posterior to the carotid sheath. This part of the sympathetic system receives no white rami communicantes, its preganglionic fibers being derived from white rami which enter the thoracic portion and then turn upward.

A. The superior cervical ganglion is an oval structure about two centimeters long which lies in front of the transverse processes of the second and third cervical vertebrae. Externally it is in relation with the vagus and anteriorly with the internal carotid artery. It receives, via the association cord, preganglionic fibers from the upper thoracic segments of the spinal cord. All the preganglionic fibers which arrive at this ganglion, end there, none, in all probability, going farther. Its branches are:

1. Four gray rami communicantes to the first, second, third and fourth cervical nerves.

2. The so-called communicating branches to the ganglion petrosum of the ninth nerve, to the ganglia jugulare and nodosum of the tenth, and to the twelfth nerve.

3. The pharyngeal branch, which runs downward and inward to the surface of the middle constrictor muscle of the pharynx to take part in the formation of the pharyngeal plexus.

4. The superior cervical cardiac nerve, which starts from two or three rootlets from the ganglion and descends in the carotid sheath

to the base of the neck. The right nerve continues downward in association with the innominate artery, reaches the aorta and joins the deep cardiac plexus. The left nerve enters the thorax in company with the common carotid artery, then joins the aorta and finally contributes to the superficial cardiac plexus. The superior cardiac nerve also gives off a pretracheal twig which lies in front of the trachea and goes to the pericardium and the anterior pulmonary plexus.

5. The vertebral branches, which are distributed to the upper cervical vertebrae and their ligaments.

6. The external carotid branch, which is really a series of fibers forming a plexus around the artery of that name. The plexus supplies all the branches of this artery. In addition those branches which are carried by the superior thyroid artery probably supply the thyroid gland. From the plexus on the facial artery a branch is given off as the sympathetic root to the submaxillary ganglion (q.v.). From the plexus on the middle meningeal artery, a nerve, the smallest deep petrosal, forms the sympathetic root of the otic ganglion.

7. The internal carotid nerve, so-called, which is a large plexus surrounding the internal carotid artery and accompanying it in its intracranial course. It supplies vasomotor nerves to this artery and to all its terminal branches. On emerging from the carotid canal it divides into two portions: the carotid plexus which lies on the outer side of the artery and the cavernous plexus which lies toward the inner side, many fibers connecting the two plexuses.

The carotid plexus gives off the following branches:

(*a*) A branch to the sixth nerve, perhaps destined for the sympathetic innervation of the external rectus muscle.

(*b*) Branches to the Gasserian ganglion.

(*c*) The great deep petrosal nerve, which leaves the artery to run forward and join the great superficial petrosal nerve at the posterior end of the Vidian canal. The Vidian nerve, thus formed, traverses the canal and then enters the sphenopalatine ganglion, of which the great deep petrosal nerve is the sympathetic root.

(*d*) The small deep petrosal nerve, sometimes called the caroticotympanic nerve, which runs backward and upward to enter the tympanic cavity. Here, in conjunction with Jacobson's nerve of the glossopharyngeal, it forms the tympanic plexus which supplies the mucous membrane of the middle ear.

The branches of the cavernous plexus are:

(*a*) A branch to the third nerve.

(*b*) A similar branch to the fourth nerve.

(Both of the above probably have the same functions as the homologous fibers to the sixth nerve from the carotid plexus.)

(*c*) A branch to the ophthalmic division of the fifth nerve.

(*d*) The sympathetic root of the ciliary ganglion, a nerve which enters the orbit through the sphenoidal fissure and after traversing the ciliary ganglion forms the sympathetic constituent of the branches of the latter.

(*e*) Several fine fibers, which run directly to the pituitary gland.

B. The middle cervical ganglion is a rather inconstant structure found at the level of the transverse process of the sixth cervical vertebra. It gives off the following branches which may arise from the association cord when the ganglion is absent:

1. Gray rami communicantes to the fifth and sixth cervical nerves.

2. The subclavian loop, which runs downward in front of the subclavian artery, then beneath the latter structure and finally behind it to join the association cord or the inferior cervical ganglion. Fibers are given off for the innervation of the subclavian artery and there is also a communicating branch to the phrenic nerve. This loop may be regarded as a branch of the middle cervical ganglion or one may conceive of the subclavian artery as splitting the association cord into an anterior and posterior division.

3. The thyroid branches, which form a plexus around the superior thyroid artery and supply the gland.

4. The middle cervical cardiac nerve which runs downward and receives communicating fibers from the superior cervical cardiac nerve and from the recurrent laryngeal. The right nerve passes in front of, or behind, the subclavian artery to the front of the trachea and then, lying behind the arch of the aorta, enters the deep cardiac plexus. The left nerve runs between the subclavian artery and the common carotid, behind the arch of the aorta, and also enters the deep cardiac plexus.

C. The inferior cervical ganglion lies at the level of the transverse process of the seventh cervical vertebra lateral to the body of the vertebra and in front of the neck of the first rib. It may be fused with the first thoracic ganglion. Its branches are:

1. Gray rami communicantes to the seventh and eighth cervical nerves.

2. A communicating branch to the recurrent laryngeal nerve.

3. The inferior cervical cardiac nerve, which runs downward and inward, behind the subclavian artery. It then communicates with the recurrent laryngeal and middle cervical cardiac nerves and participates in the formation of the deep cardiac plexus.

4. The vertebral plexus, formed of a series of fibers which leave the inferior ganglion and form a plexus around the vertebral artery and its branches.

II. The Thoracic Division

The thoracic part of the ganglionated cord is the downward continuation of the cervical trunk. The cord lies lateral to the bodies of the vertebrae, anterior to the heads of the ribs, and extends from the first to the last rib, leaving the thorax through the aperture between the intermediate and lateral crura of the diaphragm.

The segmental character of the sympathetic system is most clearly displayed in the thoracic portion, which consists of twelve ganglia, one for each rib, connected by the so-called association cord. Each ganglion receives a white ramus communicans from the corresponding ventral root and sends a gray ramus to each thoracic spinal nerve. The fibers comprising the white rami do not all end in the ganglia opposite their point of exit. There are, in fact, four possible courses for them to pursue, all of which actually occur. In the first place, the fibers may end in the nearest ganglion coming into synaptic union with the cells which constitute that ganglion. Or, they may turn upward to end in the more cephalic ganglia of the thoracic or cervical trunk. The cervical portion of the sympathetic system receives no white rami and consequently derives all its preganglionic fibers from white rami which have entered the sympathetic trunk at or below the first thoracic segment. In the third place, the fibers may descend in the thoracic, or even lumbar or pelvic portion of the trunk, before terminating in these lower ganglia, the impulse then being relayed via gray rami to the lower spinal nerves. Finally, the fibers of the white rami may follow a shorter or longer course through the association cords and through several ganglia and then leave the main trunk to terminate eventually in the intermediate or terminal ganglia.

The branches of the thoracic portion of the sympathetic system are as follows:

1. The white rami communicantes, just described, which carry not

only preganglionic efferent fibers but also afferent fibers, derived in all probability from cells in the dorsal root ganglia.

2. The gray rami communicantes, one or more of which arise from each ganglion and pass to the corresponding thoracic nerve. Through this nerve they are distributed to the sebaceous and sweat-glands of the skin, to the smooth muscle of the skin, to the blood-vessels which lie in the territory supplied by the nerve in question and also, probably, to the striated muscles of the same region.

3. The pulmonary branches, the fibers of which arise from the second, third and fourth thoracic ganglia and run forward to the root of the lung. Here they are joined by similar fibers from the opposite side and by branches from the vagus nerve. In this way the posterior pulmonary plexus is formed, which proceeds distally following the course of the bronchial tree and innervating the musculature of the bronchi, the mucous membrane of the latter as well as the accompanying blood-vessels. Numerous connections exist between the posterior and the anterior pulmonary plexus (q.v.).

4. The branches given off from the first to the fifth thoracic ganglia. These branches run anteromedially and, combining to form a network, spread out over the aorta as the plexus of the thoracic aorta.

5. The great splanchnic nerve, which is formed by the union of fibers derived from the fifth to the ninth thoracic ganglia. The nerve-trunk thus formed, courses inward, forward and downward, leaves the thoracic cavity between the medial and intermediate crura of the diaphragm and terminates in the upper pole of the semilunar ganglion.

6. The small splanchnic nerve, composed of branches from the ninth and tenth or tenth and eleventh ganglia. It follows the same course as the great splanchnic nerve and after entering the abdominal cavity ends in the aorticorenal ganglion.

7. The least splanchnic nerve, derived from the eleventh or twelfth ganglion, which leaves the thorax with the main trunk of the sympathetic nervous system. Its fibers are distributed to the renal plexus.

As was described above, the major constituents of the splanchnic nerves are (medullated) preganglionic fibers destined to end around cells of more distal ganglia, while a few of the fibers are postganglionic and in this case run without further interruption to their appropriate end-organs. In addition these nerves also contain fibers which carry afferent impulses from the viscera and which run without interruption

through the ganglionated cord, the white rami, and the dorsal roots, to enter the spinal cord at various levels.

III. The Lumbar Division

The lumbar part of the sympathetic trunk is composed of a variable number of ganglia, usually four, connected by an association cord which above is the downward continuation of the thoracic trunk and below becomes the sacral portion. In the lumbar region the two trunks tend to approach each other with the result that they lie anterior to the bodies of the lumbar vertebrae, behind the aorta on the one side and the vena cava on the other. The branches of this subdivision are:

1. White rami communicantes, which are received from only the first and second and occasionally the third lumbar nerves. Probably none of the fibers which constitute these rami take an ascending course; they either end around cells in the ganglia opposite their respective points of exit or turn downward to end in the lower ganglia of the lumbar or sacral part of the chain.
2. Gray rami communicantes, which are given off to each lumbar cerebrospinal nerve and subserve the same functions as do the post-ganglionic fibers which run with the somatic nerves of the cervical and thoracic segments.
3. Branches to the aortic plexus, the fibers of which run forward and mingle with the other vegetative nerves which surround the abdominal aorta.
4. Branches to the hypogastric plexus, which run downward in front of the common iliac arteries and assist in the formation of the hypogastric plexus lying in front of the sacrum.
5. Several small fibers, distributed to the vertebrae and to the adjacent ligamentous structures.

IV. The Sacral Division

The sacral division of the sympathetic system, the most inferior, consists of four ganglia joined to each other and to the lumbar part by an association cord. The two sacral chains lie on the anterior surface of the sacrum behind the great vascular trunks and internal to the sacral foramina. They run downward and inward and finally join each other in the single, unpaired coccygeal ganglion which is

found in front of the coccyx. The sacral chain receives no white rami. Its branches are:

1. Gray rami to each sacral nerve.
2. Branches which run forward to participate in the formation of the pelvic plexus.
3. Small filaments to the sacrum, coccyx and their ligaments.

THE PARASYMPATHETIC SYSTEM

The second subdivision of the vegetative nervous system is the parasympathetic system. The cell-bodies of the preganglionic fibers of this system do not form a single column as is the case with the sympathetic system but are broken up into islands which are found in the midbrain, medulla, and sacral portion of the spinal cord. The ganglia associated with this system are those of the head, to be described presently, and the so-called terminal ganglia which exist in connection with the vagus and the sacral contingent. In the case of these terminal ganglia there is much less tendency for the constituent cells to be aggregated into large masses. These cells, which give rise to the postganglionic fibers of the parasympathetic system, are found, as their name implies, in or near the walls of the structures which they innervate.

The cranial outflow of the parasympathetic system is as follows:

I. The Midbrain Contingent

The preganglionic fibers of this part of the parasympathetic system are axones of small cells lying in the oculomotor complex in the central gray of the midbrain. Most authorities believe that these cells constitute the median anterior nuclei of the complex, the so-called Edinger-Westphal nuclei, though Winkler dissents from this view, feeling that there is not yet sufficient evidence to enable one to state definitely what cells are the trophic centres of the preganglionic fibers in question. In any event, the fibers leave the neuraxis in company with the somatic portion of the oculomotor nerve. They travel with this nerve as far as the posterior part of the orbit, where they leave it, to enter the posterior portion of the ciliary ganglion. This is a small ganglion about 2 mm. long which lies near the apex of the orbit toward the outer side of the optic nerve. It contains multipolar, vegetative cells whose dendrites receive the terminations of the preganglionic fibers arriving via the oculomotor nerve. This branch

from the third nerve, the so-called motor root of the ganglion, must therefore be regarded as a white ramus communicans. In addition to this contribution from the oculomotor nerve two other sets of nerve-fibers enter the ciliary ganglion. One of these consists of fibers from the ophthalmic plexus which have come by way of the cavernous plexus from the superior cervical ganglion and constitute the sympathetic root. The other is derived from the nasal branch of the ophthalmic division of the trigeminus and is termed the sensory root. As far as it is known, the fibers of the two latter categories are not interrupted in the ganglion but simply pass through it.

The emergent branches of the ciliary ganglion, called the short ciliary nerves, are about twenty in number and run directly forward to the bulbus oculi, one group lying above and the other below the optic nerve. These fibers pierce the sclera and then continue their course between the sclera and chorioid. The short ciliary nerves are thus seen to be composed of afferent fibers which are derived from the trigeminal nerve and which supply the interior of the eye; of postganglionic sympathetic fibers; and finally of postganglionic parasympathetic fibers whose cell-bodies lie in the ciliary ganglion and which supply the ciliary muscle and the sphincter iridis.

II. The Bulbar Contingent

Three nerves carry the preganglionic fibers of this portion of the parasympathetic system, namely, the facial, glossopharyngeal and vagus.

A. The facial nerve and its associated ganglia. In addition to supplying the muscles of the face, the seventh nerve carries both efferent and afferent vegetative fibers. The cells of origin of these preganglionic fibers have not been identified with certainty, but probably lie dorsal to the facial nucleus in the brain-stem. Impulses are distributed to the lacrimal and submaxillary and sublingual glands, as well as to the mucous membranes and probably to the blood-vessels of the head in the following manner:

1. Fibers leave the neuraxis in company with the motor fibers of the facial nerve. They leave this nerve in the facial canal and, like the great superficial petrosal nerve, traverse the hiatus Fallopii in the petrous portion of the temporal bone. This nerve then runs forward beneath the Gasserian ganglion, crosses the middle lacerated foramen and running outside of the internal carotid artery enters the

Vidian canal. At this point it is joined by the great deep petrosal nerve, a derivative of the cervical sympathetic nerve. The common trunk, which is now called the Vidian nerve, goes through the canal of that name and emerges in the sphenomaxillary fossa where it almost immediately enters the sphenopalatine ganglion. This is a small, flattened body, composed of autonomic cells, which lies in the upper part of the fossa. In addition to receiving parasympathetic and sympathetic fibers via the Vidian nerve, it receives also two or three branches, the sphenopalatine nerves, from the maxillary division of the trigeminal nerve. These nerves constitute its so-called sensory root. The sympathetic and sensory elements simply traverse the ganglion without interruption. The parasympathetic fibers of the Vidian nerve, however, are to be regarded as collectively constituting a white ramus communicans. As preganglionic fibers, therefore, they terminate in synaptic union with the cells of the sphenopalatine ganglion whose axones leave the ganglion as postganglionic fibers.

The branches of the sphenopalatine ganglion are:

(*a*) The orbital, which enters the orbit via the sphenomaxillary fissure to supply the lining of the sphenoid and ethmoid sinuses.

(*b*) The large posterior palatine, which enters the large posterior palatine canal and emerges on the inferior surface of the hard palate. There it runs forward supplying the mucous membrane of the hard palate and also that of the inner surface of the gums of the upper jaw. While in the canal it gives off branches which innervate the mucous membrane of the inferior turbinate.

(*c*) The small posterior palatine nerve, running downward through the small posterior palatine canal to supply the tonsil and the mucous membrane of the soft palate.

(*d*) In addition the accessory posterior palatine fibers, which descend through the accessory posterior palatine canals and end in the tonsil and mucous membrane of the soft palate.

(*e*) The posterior superior nasal nerve, running through the sphenopalatine foramen into the nasal fossa to supply the upper posterior portion of the lateral wall of the nasal fossa.

(*f*) The nasopalatine nerve, which also enters the nasal fossa by way of the sphenopalatine foramen. It then runs forward in a groove in the vomer, finally reaching the anterior palatine canal. The right nerve enters the posterior canal and the left, the anterior,

and then they reach the anterior portion of the mucous membrane of the hard palate which they supply.

(*g*) The pharyngeal branch, passing backward through the pterygopalatine canal, supplies the mucous membrane of the nasopharynx around the fossa of Rosenmüller.

All these branches of the sphenopalatine ganglion probably contain fibers of three types: (1) Sensory fibers from the trigeminal nerve, not interrupted in the ganglion. (2) Postganglionic sympathetic fibers whose cell-bodies lie in the superior cervical ganglion; also not interrupted in the ganglion. (3) Postganglionic parasympathetic fibers whose cells of origin lie in the ganglion.

2. Other fibers of parasympathetic character leave the facial nerve with the chorda tympani. This nerve leaves the facial above the stylomastoid foramen, enters the iter chordae posterius and traverses the tympanic cavity which it leaves through the iter chordae anterius. It continues downward and forward and joins the lingual nerve. In the vicinity of the submaxillary ganglion the preganglionic, vegetative constituents of the nerve make their departure from the main trunk and enter the ganglion as its so-called motor root. The submaxillary ganglion is a small structure about 2 mm. in diameter which lies on the hyoglossus muscle above the submaxillary gland and below the lingual nerve. Its motor root consists of the fibers just described. These fibers end in the ganglion around its constituent cells, which then relay the impulses received to their postganglionic fibers. The sympathetic root is a branch from the plexus on the facial artery, as already described, and the sensory root is derived from the trigeminal nerve via the lingual. The branches of this ganglion possess the same mixed character as those of the other vegetative ganglia of the head, i.e., they are composed of postganglionic parasympathetic fibers, the interruption of the impulse having occurred in the ganglion; of postganglionic sympathetic fibers, the interruption of whose impulses occurred in the superior cervical ganglion and which have traversed the submaxillary ganglion without anatomical or physiological alteration; and, finally, of sensory trigeminal fibers which have also merely passed through the ganglion. These branches are:

(*a*) Fibers which go directly to the adjacent submaxillary gland.

(*b*) Fibers to the duct of the gland and to the mucous membrane of the floor of the mouth.

(*c*) Fibers to the sublingual gland, distributed by way of the lingual nerve.

B. The parasympathetic relations of the glossopharyngeal nerve. Dorsal and a little lateral to the cephalic part of the nucleus ambiguus are found small nerve-cells whose axones are probably to be regarded as preganglionic parasympathetic fibers. This collection of cells is termed the nucleus salivarius inferior. The fibers make their exit from the neuraxis with the ninth nerve, leaving the latter at the level of the petrous ganglion as the tympanic nerve. This nerve enters the tympanic cavity by a small foramen between the jugular fossa and the carotid canal. After entering the cavity it breaks up into fibers which unite with similar fibers from the small deep petrosal nerve to form the tympanic plexus, a network of fibers which lies on the promontory. In this way the mucous membrane of the middle ear is supplied. The fibers of the plexus then condense again and are joined by a branch from the geniculate ganglion of the facial nerve. In this the small superficial petrosal nerve is formed. This nerve leaves the tympanic cavity by passing through a canal in the petrous portion of the temporal bone, entering the cranial cavity lateral to the hiatus Fallopii. It then traverses the greater wing of the sphenoid bone and thus reaches the otic ganglion.

This is a small ganglion, composed of vegetative cells, which lies below the foramen ovale internal to the mandibular nerve. The sympathetic root has been described above as consisting of fibers from the plexus of the middle meningeal artery. The ganglion receives a contribution from the internal pterygoid nerve which has been described as the motor root. It seems more probable, however, that the motor root is constituted by the small superficial petrosal nerve and that the sensory root is contributed by the trigeminal as is the case in the other cranial ganglia of the vegetative system. The branches of the ganglion are:

1. Fibers to the auriculotemporal nerve, which terminate in the parotid gland.

2. Fibers to nerves supplying adjacent muscles, possibly the sympathetic contribution to these muscles.

3. A branch to the chorda tympani.

C. The vagus nerve. The most important parasympathetic structure connected with the medulla is the vagus nerve. This nerve has both somatic and splanchnic components. By way of the latter

are supplied, through the intermediation of suitable ganglia, the heart, the smooth muscle and glands of the gastro-intestinal tract as far as the descending colon, the smooth muscle and probably glands of the respiratory tract and the accessory glands of digestion, such as the pancreas and liver, as well as the blood-vessels to these structures. These organs receive both an efferent and an afferent supply via the vagus. Since there are intercalated ganglia in the pathway of impulses to these structures, the vagus may be looked upon as an extended white ramus communicans.

The cells concerned with the parasympathetic portion of the vagus, form the dorsal motor nucleus of the part of the vagus lying beneath the trigonum vagi in the medulla. Other cells which may lie in the reticular formation, dorsal to the nucleus ambiguus, probably send preganglionic fibers also into this nerve.

The vagus leaves the lateral aspect of the medulla by several rootlets which unite to form a common trunk. This trunk leaves the cranial cavity through the middle division of the jugular foramen where the ganglion jugulare is seen. Immediately below this is encountered the ganglion nodosum. These ganglia are composed of "sensory" cells comparable to those of the dorsal root ganglia of the spinal nerves. Some authorities believe that the ganglion jugulare contains cells of fibers which convey cutaneous and proprioceptive impulses, while the cells of the ganglion nodosum are concerned with afferent impulses from the viscera.

Course of the vagus nerve:

The vagus descends in the neck in the carotid sheath between the internal jugular vein and the internal or common carotid artery. Entering the thorax the right vagus lies in front of the subclavian artery and behind the superior vena cava. It continues downward, lateral to the trachea and at the root of the lung spreads out into numerous fibers which form the posterior pulmonary plexus. Two trunks emerge from the lower part of the plexus and turn inward and downward till they reach the esophagus. They join similar branches from the left vagus and again subdivide to form the esophageal plexus which invests the esophagus as far as the diaphragm. Near the diaphragm the two trunks again become distinct and the right vagus, lying on the posterior aspect of the esophagus, enters the abdomen where it divides into its terminal branches.

The left vagus passes behind the left innominate vein, runs anterior

to the aorta and then turns downward and backward to the root of the lung. It, too, forms the posterior pulmonary plexus and the esophageal plexus and leaves the thorax as a single trunk lying on the anterior aspect of the esophagus. On entering the abdominal cavity it sends branches to the anterior surface of the stomach and to the liver.

Branches of the vagus nerve:

1. The pharyngeal nerve, one or more twigs of which leave the ganglion nodosum and run downward and inward. Over the middle constrictor of the pharynx they ramify with the pharyngeal branches of the ninth nerve and of the superior cervical ganglion to form the pharyngeal plexus.

2. The superior laryngeal nerve, also arising from the ganglion nodosum and supplying the mucous membrane of the larynx. It sends a branch to the superior cervical cardiac nerve from the sympathetic system.

3. The superior cervical cardiac branch, leaving the upper part of the vagus and descending along the side of the trachea to end in the deep cardiac plexus.

4. The inferior cervical cardiac branch, leaving the vagus at the root of the neck. The right nerve joins the deep cardiac plexus and the left the superficial plexus.

5. The recurrent laryngeal nerve, which is only partly vegetative in function. Its parasympathetic distribution is:

(*a*) Cardiac branches, which go to the deep cardiac plexus.

(*b*) A tracheal branch.

(*c*) An esophageal branch.

(*d*) A communicating branch to the inferior cervical ganglion.

6. The thoracic cardiac branches, which on the left are the cardiac branches of the recurrent laryngeal nerve, described above. On the right they arise both from the vagus and from the recurrent laryngeal. On both sides they go to the deep cardiac plexus.

7. The anterior pulmonary branches, arising near the root of the lungs. Branches from the two sides unite to form the anterior pulmonary plexus.

8. The posterior pulmonary branches, arising at about the same level and, with those of the opposite side and fibers from the sympathetic nerve, forming the posterior pulmonary plexus.

9. The esophageal branches, the upper branches of which are derived from the right vagus and the left recurrent laryngeal. The lower branches are the esophageal plexus described above.

10. The pericardial branches, supplying the pericardium in its upper portion by twigs from the vagi, and in its lower and posterior part by branches from the esophageal and posterior pulmonary plexuses.

11. The abdominal branches, which are the terminal branches of the vagi. The right vagus spreads out along the lesser curvature of the stomach as the posterior gastric plexus which supplies the posterior aspect of the stomach. In addition this plexus sends a large contribution to the celiac plexus and eventually to practically all the plexuses of the abdomen.

The left vagus ramifies as the anterior gastric plexus which supplies the anterior surface of the stomach. Its terminal branches participate, in conjunction with sympathetic fibers, in the hepatic plexus which surrounds the hepatic artery and supplies the liver, etc.

III. The Sacral Outflow

The cell-bodies of the preganglionic fibers form two columns in the spinal cord. One, the nucleus sympathicus lateralis inferior or nucleus sympathicus sacralis, occupies the intermedio-lateral portion of the gray matter and extends from the second sacral segment through the remaining portions of the cord. The other, the nucleus sympathicus medialis inferior or nucleus sympathicus lumbosacralis, lies in the medial part of the ventral horn and extends from the fourth lumbar segment down to the end of the spinal cord. In the lower segments of the cord these two columns fuse with each other and occupy most of the ventral horn. The axones of these cells make their exit from the spinal cord via the second and third sacral nerves in most instances. These fibers enter without interruption the visceral branches of the pudendal plexus and run to the pelvic plexus of which they form a part. They are thus to be regarded as the equivalent of white rami communicantes. They constitute the parasympathetic supply for the descending colon, organs of the pelvis and external genitalia, being physiologically equivalent to the vagus, which gives parasympathetic fibers to the upper viscera.

THE PLEXUSES OF THE THORAX, ABDOMEN AND PELVIS, WITH THE COLLATERAL GANGLIA OF THE SYMPATHETIC AND THE TERMINAL GANGLIA OF THE PARASYMPATHETIC NERVOUS SYSTEMS

The plexuses of the vegetative nervous system are the means by which visceral fibers are distributed to the organs which they innervate. Particularly in the abdominal cavity these plexuses as a usual thing surround blood-vessels. In general, they contain three types of fibers: first, sympathetic postganglionic fibers; second, parasympathetic preganglionic fibers. (The impulse carried by these fibers is interrupted in the terminal ganglia before affecting the end-organs.) The third are afferent fibers from the viscera, which probably run over both sympathetic and parasympathetic nerves to reach the central system.

1. The Cardiac Plexuses

The superficial plexus lies in the arch of the aorta between the right pulmonary artery and the remains of the ductus arteriosus. It is composed of sympathetic fibers carried by the left superior cervical cardiac branch of the superior cervical ganglion, and also of parasympathetic fibers which run in the left inferior cervical branch of the vagus. The latter fibers end in their terminal ganglion, the ganglion of Wrisberg, which lies in the plexus. Fibers contribute to the formation of the right coronary plexus, the left half of the deep cardiac plexus and the left half of the anterior pulmonary plexus.

The deep plexus lies behind the aortic arch, above the pulmonary artery, with the trachea posterior. The right half of the plexus is formed by the superior, middle and inferior cervical cardiac branches of the sympathetic and by all the cardiac branches of the vagus (parasympathetic). The left half has the same constitution, with the exception of the left superior cervical cardiac branch of the sympathetic and the left interior cervical branch of the vagus. The left half receives in addition fibers from the superficial plexus.

The right half of the deep plexus is continued as the anterior coronary plexus; the superficial plexus also contributes to this. The fibers follow a downward course along the ascending aorta to the heart to which they are distributed along the coronary artery.

The right anterior pulmonary plexus also is reinforced by branches from the right half of the plexus.

2. The Pulmonary Plexuses

The anterior plexus is formed by branches from the vagus, from the cardiac plexus and from the posterior pulmonary plexus. It is situated over the anterior aspect of the root of the lung.

The posterior plexus is composed of sympathetic fibers from the second, third and fourth thoracic ganglia, of branches from the vagus and of communicating branches of the anterior plexus. Both plexuses follow the bronchi and blood-vessels in their ramifications through the lungs. Along the course of the plexus and its branches occur numerous small collections of vegetative cells which represent the terminal ganglia of the parasympathetic components.

3. The Esophageal Plexus

The esophageal plexus is formed by the union of small branches from the splanchnic nerves and the inferior ganglia of the thoracic cord, and by the numerous branches into which the two vagi subdivide. It surrounds the esophagus throughout the posterior mediastinum.

4. The Solar Plexus

This plexus lies on the abdominal aorta, above the pancreas and around the celiac axis, between the adrenal glands, and behind the stomach. It is composed of two chief elements. The first of these comprises the semilunar ganglia, two large collections of vegetative cells which lie at the upper margin of the solar plexus and are connected with each other by fibers passing above and below the celiac axis. The inferolateral portion of each semilunar ganglion is termed the aorticorenal ganglion, while a part situated at the foot of the superior mesenteric artery is known as the superior mesenteric ganglion. The semilunar ganglia are the largest collateral or prevertebral ganglia of the sympathetic system. The great splanchnic nerve terminates partially in the upper pole of each, while the aorticorenal ganglia receive the small splanchnic nerves. In addition, the right vagus nerve enters the ganglia, but its fibers are not interrupted, merely passing through to be distributed to the various plexuses that arise in the vicinity.

The second element in the solar plexus is the celiac plexus. This takes its name from the artery which it surrounds. Its branches are:

(*a*) The gastric plexus, which is distributed by the stomach via the gastric artery.

(*b*) The hepatic plexus, which follows the course of the hepatic artery to the liver, receiving on the way a contribution from the left vagus via the anterior gastric plexus. It also innervates the stomach and duodenum by following the appropriate branches of the hepatic artery. Furthermore, fibers are given off to the right suprarenal plexus.

(*c*) The splenic plexus, which surrounds the splenic artery and is distributed with the latter.

The three foregoing subdivisions of the celiac plexus are composed of postganglionic sympathetic fibers which are the axones of cells lying in the semilunar ganglia or in the detached portions of the latter which are usually found in the celiac plexus, and of preganglionic parasympathetic fibers derived chiefly from the right vagus. The terminal ganglia of the latter are to be found, as far as the gastro-intestinal tract is concerned, in the so-called plexuses of Auerbach and of Meissner. These are collections of vegetative cells which lie between the longitudinal and circular muscular coats of the intestine or in the submucosa. These cells receive the preganglionic vagus, parasympathetic fibers; their axones, which are postganglionic fibers, go to the muscular, vascular and glandular elements of the gastro-intestinal tract.

Cells with similar functions, though with less distinctive anatomical patterns, are found in the other viscera and are to be regarded as terminal ganglia of the parasympathetic system.

The phrenic plexus is the most cephalic division of the solar plexus. It surrounds the phrenic artery on each side and is distributed to the diaphragm. Each plexus sends fibers to the adrenal gland. On the right side, on the inferior surface of the diaphragm, occurs the small phrenic ganglion which sends branches to the adrenal gland, the hepatic plexus and the vena cava.

The suprarenal plexus is really the lateral extension of the semilunar ganglion and supplies the adrenal gland on each side.

The renal plexus is composed of fibers from the aorticorenal ganglion, the least splanchnic nerve, the aortic and suprarenal plexuses. It has the same constitution as that of other plexuses,—vagal fibers probably also being present. The plexus surrounds the renal artery along whose course are also found the small renal ganglia, and

supplies the vessels and parenchyma of the kidney. In addition, this plexus sends fibers to the ureter and also aids in the formation of the spermatic or ovarian plexuses.

The spermatic plexus, formed by the renal and aortic plexus, surrounds the spermatic artery and follows the course of the latter to the scrotum. It is joined by derivatives of the pelvic plexus which innervate the vas deferens.

The ovarian plexus has a similar origin. Surrounding the ovarian artery, it innervates the ovaries, Fallopian tubes, uterus and broad ligaments.

5. The Superior Mesenteric Plexus

The origin of this plexus lies anterior to the aorta, between the celiac axis above and the superior mesenteric artery below and may be regarded as the caudal extension of the solar plexus. Its sympathetic fibers are derived from the semilunar ganglia, the celiac plexus and the superior mesenteric ganglion. The latter, another prevertebral or collateral ganglion, lies just below and to the right of the point of origin of the superior mesenteric artery. The parasympathetic fibers from the right vagus come by way of the celiac plexus. The superior mesenteric plexus follows the artery and all of its subdivisions, innervating the small intestine and the large intestine as far as the descending colon.

6. The Aortic Plexus

The aortic plexus consists of two nerve-trunks, one on each side of the anterior aspect of the aorta, between the superior mesenteric and inferior mesenteric arteries. These trunks are connected across the midline by many fibers. Contributing fibers are received from the semilunar ganglia, the renal and superior mesenteric plexuses, as well as from the lumbar ganglia of the sympathetic cord. The plexus sends branches to the suprarenal, renal and spermatic or ovarian plexuses, as well as to the inferior mesenteric plexus and also to the aorta and inferior vena cava.

7. The Inferior Mesenteric Plexus

The inferior mesenteric plexus arises from the aortic plexus at the level of the inferior mesenteric artery. Fibers are also contributed by the inferior mesenteric ganglion. These fibers are all sympathetic

in character. It is probable that preganglionic parasympathetic fibers from the pelvic plexus follow an ascending course through the hypogastric plexus to participate in the formation of the inferior mesenteric. The plexus follows the course of the artery supplying the descending colon, sigmoid and rectum.

8. The Hypogastric Plexus

The hypogastric plexus, the downward extension of the aortic, is formed by branches from the aortic plexus and from the lumbar ganglia. It lies between the common iliac vessels and, with the pelvic plexuses, supplies the organs of the pelvis.

9. The Pelvic Plexus

This is a paired structure lying one on each side of the rectum and surrounding the internal iliac artery. The sympathetic constituents are derived from the hypogastric plexus and the sacral ganglia. Parasympathetic fibers reach it by way of the visceral branches of the pudendal plexus. In the plexus occur numerous small ganglia, near the walls of the various structures innervated, and these are to be classified as terminal ganglia of the sacral portion of the parasympathetic system.

The branches of the pelvic plexus follow the branches of the internal iliac artery and are called:

(*a*) The hemorrhoidal plexus to the rectum.

(*b*) The vesical plexus to the bladder, vas deferens and seminal vesicle.

(*c1*) The prostatic plexus. After supplying the prostate gland, branches continue forward as the cavernous plexus which supply the penis with large and small cavernous nerves.

(*c2*) The uterine plexus to the uterus and the vaginal plexus to the vagina and clitoris.

CHAPTER IV

THE CENTRAL REPRESENTATION OF THE SYMPATHETIC NERVOUS SYSTEM AS INDICATED BY CERTAIN PHYSIOLOGICAL FINDINGS[1]

PHILIP BARD, Ph.D.

INTRODUCTION

BY THE term sympathetic nervous system is usually meant that extensive and diffuse group of outlying neurones which are connected through white rami communicantes with the thoracic and lumbar regions of the spinal cord. Only occasionally is the expression used to include structures more central than the cell-bodies of the connector or preganglionic neurones which, as Gaskell and others (31) have shown, lie in the lateral horns of the thoracic and lumbar segments of the cord. It has long been recognized that the physiological activity of these peripheral nerve-fibers and ganglion-cells is entirely under the control of the central nervous system and there is available evidence for the existence of what appear to be fairly definite central mechanisms which are concerned in the discharge of nerve-impulses over preganglionic sympathetic neurones. Thus one may speak of a central representation of the sympathetic nervous system.

Historically both the outlying system and its central control have had their special emphasis. At times the notion that the sympathetic represents an autonomous peripheral nervous system has received notable support. Long known as the intercostal nerve, it was christened *le grand sympathique* by Winslow (76) in 1732, because that anatomist wished to accentuate the ancient view that these nerves, acting independently of the central nervous system, mediated the sympathies of the body. The idea that the sympathetic system possesses a certain autonomy of function reached its fullest development at the hands of Bichat who stated (9) that he regarded the central nervous system of "la vie organique," as including the functions of

[1] From the Physiological Laboratory, Princeton University.

assimilation, circulation and excretion. Nevertheless from the earliest times the necessity for some connection between brain and viscera had been impressed upon all who gave thought to the visceral changes so obviously accompanying emotional states. In the light of modern work on the sympathetic nervous system it is interesting to see how anciently and how often the opinion was expressed that the sympathetic nerves mediate the influence which the emotions exert upon the viscera.

Early anatomists traced the intercostal nerves up into the cranial region and were persuaded that they arose from filaments of the fifth and sixth pairs of cranial nerves ((34), iv, 223). This view persisted in spite of the fact that many investigators had distinguished the rami communicantes. These structures are plainly seen in the remarkable Tabula XVIII of Eustachius, prepared in 1552, and they were described by many writers up to and including von Haller (34). Pourfour du Petit (60) writing in 1727, was the first to contest the cerebral origin of the intercostal nerves. He observed the miosis and other ocular effects produced by section of the cervical sympathetic nerve and correctly concluded that the intercostal system supplies an influence which passes from below upwards.

Many early writers thought of the cerebral control of the viscera as being confined to a single division of the central nervous system. Thomas Willis, for example, located it in the cerebellum (51, 75); but in the absence of any knowledge of the exact effects produced by the diffusely distributed sympathic fibers, there was no real basis for a definite central localization of sympathetic functions.

Du Petit's work remained for over a century the only experimental demonstration of a definite peripheral effect. When finally the various actions of the sympathetic fibers upon the organs innervated were worked out during the second half of the last century, there developed a real knowledge of the relations which exist between the outlying parts of this system and the various divisions of the central nervous system.

Claude Bernard's contributions to the physiology of the sympathetic nervous system were important. He showed that vasoconstrictor fibers are sympathetic and that these nerves exert a constant effect upon the blood-vessels (8). In his tendency to restrict their origin to the thoracic and lumbar segments of the spinal cord he anticipated the classical work of Gaskell and Langley. These important con-

tributions were soon followed by German work which established as an experimental fact the early supposition that sympathetic nerves act upon the heart. The erection of the hairs must have long been noticed as a symptom of emotional excitement in animals; and the dependence of this phenomenon upon the sympathetic system was demonstrated in 1870 by Moritz Schiff (68). He found that the erection of the tail hairs which occurs in a cat when that animal is confronted by a dog is abolished by the section of the lumbar sympathetic chain.

The fact that the sympathetic outflow from the central nervous system is restricted to connector neurones which arise in the thoracico-lumbar region of the cord, was definitely established in 1886 by Gaskell (31) whose work was the first to make possible a generalization in regard to the origin of the fibers of the whole autonomic system. As is well known, Gaskell's study was extended by Langley who introduced the names *preganglionic* and *postganglionic* to describe respectively Gaskell's connector neurones and those which have their cell-bodies in the sympathetic ganglia. Of special importance to the present discussion is Langley's finding that the preganglionic fibers issuing from any one spinal nerve pass to a series of lateral ganglia, usually from six to nine in number, and never to a single segmental ganglion. This morphological condition assures a diffuse discharge of nerve-impulses over postganglionic fibers and is in marked contrast to the condition found in the parasympathetic system where preganglionic fibers belonging to a definite functional group pass to ganglia situated within or close to the organ innervated, —an arrangement for the discharge of impulses to single organs. When it was subsequently determined that the glandular cells of the adrenal medulla are derived from embryonic cells having a common origin with those of sympathetic ganglia (31), that these cells receive a preganglionic sympathetic innervation (28) and that adrenin on passing into the blood-stream acts upon any tissue in the same way as do the impulses of postganglionic sympathetic fibers (52), it became clear that the adrenal medulla is an integral part of the sympathetic system and that it represents another means of producing a widespread effect when the sympathetic system is active. The fact that the sympathico-adrenal system is designed to function as a whole has been pointed out by Cannon (15). This writer has emphasized that the conditions under which the sympathetic system tends so to act are

those which demand a vigorous response to insure the maintenance of an essential bodily state or even of life itself. Such conditions include strong emotional excitement, pain, asphyxia, exposure to cold, muscular exercise, and the hypoglycemia which follows the exhibition of insulin. The work of Cannon and his collaborators has established the emergency function of the sympathico-adrenal system. It has received confirmation at the hands of a number of investigators working in diverse parts of the world and employing a variety of methods (17, 19).

Apart from its emergency function, which is characterized by a widespread discharge over all preganglionic neurones, the sympathetic system carries out other duties in the animal economy. A certain fraction of the preganglionic fibers are constantly discharging nerve-impulses, and this tonic activity is of importance in maintaining the normal level of arterial pressure, the normal rate of the heart, the size of the pupil, the position of the bulbus oculi, the degree of relaxation of the bronchial musculature and other physiological conditions. This discharge may be broken by central inhibition or augmented by central excitation. Other sympathetic paths, such as those to the sweat-glands and *erectores pilorum*, are normally at rest. Certain fractions of the preganglionic outflow may be caused to discharge either more or less while others remain unaffected.

From the foregoing remarks it is apparent that the central representation of the sympathetic system is of the following character: All parts of it are capable of reflex excitation and inhibition and much of it is in constant activity. While some parts of it seem capable of acting independently of others the marked tendency of the sympathetic system to discharge vigorously and as a whole under conditions of stress, implies the existence of some predominant central mechanism which is capable of causing a discharge of impulses over the entire series of preganglionic neurones. With these suppositions in mind one may approach the actual evidence for definite representation of the central sympathetic nervous system.

BULBAR AND SPINAL SYMPATHETIC CENTRES

The Vasoconstrictor Mechanism

Following Bernard's recognition of a tonic vasoconstrictor discharge from the central nervous system it was reported by a number of his

contemporaries that section of the spinal cord leads to a profound fall in arterial pressure (8, 37). In 1870 Dittmar (25) found that central stimulation of the sciatic nerve induces a good reflex rise in arterial pressure after separation of the medulla and cord from the rest of the brain and he, therefore, concluded that the reflex centre for vasoconstriction is situated in the bulb. A relatively exact localization of the region responsible for both the tonic activity of the vasostrictors and their reflex discharge was accomplished by Owsjannikow a year later (58). He used the method of successive transections of the brain-stem and arrived at the conclusion that this area lies between the uppermost part of the pontile region and a point lying 4 to 5 mm. above the calamus scriptorius. In rabbits it occupies a strip of the floor of the fourth ventricle about 4 mm. in length. Separation of this region from the cord is as effective in lowering arterial pressure and pressor and depressor reflex excitability as is section of the cervical cord. In 1873 Dittmar reached similar conclusions and, by means of an histological study of the brains from his animals, he connected the centre with a group of nerve-cells in the diffuse part of the superior olive (25).

Following this early work done in Ludwig's laboratory at Leipzig (54–56) no further delimitation of the vasoconstrictor centre was accomplished until the investigations of Ranson and Billingsley (63), who explored the floor of the fourth ventricle with a needle electrode. Application of the current at two points consistently produced marked changes in arterial pressure. One, not more than a millimeter in diameter and situated at the apex of the ala cinerea (at the lower margin of the area of Dittmar and Owsjannikow) is a pressor point; the other, a depressor point, is located in the area postrema just lateral to the obex (below the region of Dittmar and Owsjannikow). Sometimes a rise in pressure was obtained from the region of the facial colliculus, which corresponds to the cranial border of Dittmar's area. It is not at all certain what interpretation should be attached to these findings. It is possible that instead of being the sites of vasoconstrictor and vasodilator centres, these small areas represent points on the course of tracts connected with the true centres. Porter has maintained that there is a vasotonic centre distinct from the vasoconstrictor centre (61) and, as suggested by Ranson and Billingsley (63), the region of the facial colliculus may represent such a centre. It is true that in making his successive transections, Owsjannikow

found that the first one which encroached upon his vasomotor area caused a drop in pressure without affecting pressor or depressor reflexes. Porter's view is based upon the fact that curari will increase and alcohol decrease the effects of pressor and depressor stimulation without altering the basal height of arterial pressure. As remarked by Bayliss (6), these results do not prove the existence of separate centres, for the drugs may not act solely upon the centre itself. If the normal tone of the centre is reflex in origin, they could affect the synapses in this or other regions in such a way that their excitability is changed for artificial, but not for natural rates of afferent impulses. If on the other hand, the tone is dependent, as it may well be, upon the metabolism of the centre, it is conceivable that these drugs merely block the approach of sensory impulses set up by the artificial stimulation. In regard to the existence of a separate vasodilator centre, it may be said that Ranson and Billingsley's experiments afford the only evidence which is not wholly circumstantial. In 1908 Bayliss showed that the law of reciprocal innervation operates in the depressor reflex since this change involves central inhibition of the tone of the sympathetic vasoconstrictors as well as excitation of the non-sympathetic vasodilator nerves (6). This suggests that the vasomotor centre consists of vasoconstrictor and vasodilator elements, which may or may not be anatomically distinct.

Regardless of whether there be separate vasotonic, vasoconstrictor and vasodilator centres, it is certain that this narrowly localized central apparatus makes a definite connection with the sympathetic outflow to the arterioles. It is evidently responsible for their normal tone and its tonic discharge may be increased or decreased by afferent impulses or by changes in blood-supply (2).

Immediately after a cervical transection of the cord, there is a severe fall in the general arterial pressure and no vasomotor reflexes can be elicited. In time the pressure rises, and after some weeks it attains its normal level when large vasoconstrictor reflexes can be obtained (6, 72). That even the low height of pressure following cervical transection is partly due to a residuum of spinal vasotonic influence, is shown by the fact that this pressure is still further lowered by splanchnic section or destruction of the cord. These facts indicate that the spinal cord contains vasoconstrictor mechanisms, subsidiary to the bulbar centre, but capable, in the spinal animal, at least, of independent activity. Yet almost all the evidence in favor of the

dominance of the bulbar mechanism is based upon a comparison of the spinal with the bulbospinal preparation, and since spinal shock or recovery from spinal shock must always be a feature in the former, the contrasting of the two conditions is not the most desirable basis for the assumption that the bulbar mechanism is the dominant one in the intact animal. Until more is known about spinal shock and its disappearance, the reactions of an isolated cord cannot be compared with those of a cord which possesses its normal relations with the higher centres. That the spinal vasoconstrictor mechanism normally plays a minor rôle has been shown by Ranson (62). This investigator had previously shown that the afferent impulses producing the pressor reflex as elicited by central sciatic stimulation are carried along the cord in the apex of the posterior gray column. This part of the cord consists of the *substantia gelatinosa Rolandi* and Lissauer's tract and contains short association neurones linking one segment with another. By cutting through the apices of the posterior gray columns at the level of the first thoracic segment, Ranson found that he was able to interrupt the pathway for afferent pressor impulses without producing any paralysis or perceptible degree of spinal shock. If the pressor reflex were purely spinal, this lesion should not affect the reaction as evoked from the sciatic nerve, but should abolish the reflex from the brachial nerve. On the other hand, if the reflex were bulbar, the lesion should interrupt the spinal path connecting the sciatic afferents with the centre, but leave intact the path which ascends from the afferents of the brachial plexus. Ranson accordingly compared the results obtained by central stimulation of the brachial and sciatic nerves; he found that in each of his eight cats a good pressor reflex was obtained by faradization of the brachial nerves, but that sciatic stimulation gave no response or a slight fall of pressure in four, a slight pressor effect in three and, in one, a rise in pressure of some size, but less than that obtained from brachial stimulation. Since a given current strength applied to both the brachial and the sciatic nerves, evokes equal reflex increases in pressure, Ranson felt justified in comparing the two sets of responses. His results afford excellent evidence that the pressor reflex arc is not complete within the cord.

The Cardio-Accelerator Mechanism

Ever since the discovery of cardio-accelerator nerves, it has been possible to postulate a cardio-accelerator centre. On the other hand,

it has not been possible to assign it any definite location. Yet the sympathetic nerves which supply the heart possess tone (40) and the capacity for reflex discharge (20), properties which imply a specific central representation. As a matter of fact the medulla oblongata probably constitutes the immediate source of these discharges. Hunt (40) has reported that section of the crura cerebri does not abolish accelerator tone. While direct excitation of the floor of the fourth ventricle usually produces cardio-inhibition this effect is replaced by acceleration after section of the vagi (63) and this latter result is not affected by denervation of the adrenal glands (37).

Hunt (40) was the first to show the great importance of diminution of vagal tone in reflex accelerations of the heart and both Bainbridge (3) and von Brücke (10) have presented evidence that the law of reciprocal innervation holds in cardiac reflexes. These facts at once suggest that there is a single cardiac centre controlling and co-ordinating vagal and sympathetic discharges to the heart. Furthermore it has been suggested by Bainbridge that the circulatory reflexes which occur in sensory stimulation or during muscular exercise form a group, acting as a single reflex which can be evoked by impulses from either the periphery or the cerebral cortex. Heart and vascular reflexes are closely interconnected. Their efferent limbs are partly sympathetic, partly parasympathetic, and, if one includes the posterior root fibers concerned with vasodilatation, they are in part cerebrospinal (non-autonomic). It follows that all of the central mechanisms involved, vasoconstrictor, vasodilator, cardio-accelerator and cardio-inhibitory, are closely related physiologically and it appears that anatomically they are connected and in close juxtaposition in the medulla oblongata.

The Reflex Mechanism for Adrenal Secretion

Langley has shown that the splanchnic nerves receive their preganglionic fibers through white rami from the fifth thoracic to the second lumbar nerves (50). Consequently, the secretory fibers of the adrenal medulla must have their cell-bodies in the lateral horns of this region of the cord. Stewart and Rogoff, who have maintained that there is a constant medulli-adrenal secretion of unvarying amount, locate the centre for this activity in the upper part of the thoracic cord (71), but they have made the claim that neither this nor any other possible adrenal centre can be activated reflexly. They assert that,

aside from peripheral splanchnic stimulation, the only way in which they were able to bring about an increased secretion of adrenin (as detected by their method) was by the administration of strychnine or the intravenous injection of salts which cause a general excitation of the cord. Using the denervated heart as an indicator of medulli-adrenal secretion, Cannon and Rapport (22) obtained reflexly a secretion of adrenin which they estimated to be ten times the amount which Stewart and Rogoff suppose to be the unvarying product of the glands. Stewart states that his spontaneous constant output of adrenin is entirely under nerve-control; his quantitative estimation indicated a considerable fall in the epinephrin content of caval blood after section of the splanchnic nerves (70). In short, Stewart, while affirming the tonic activity of the central mechanism connected with the secretory nerves of the adrenal glands, denies that this mechanism can be affected by afferent impulses. Such a centre as that postulated by Stewart would indeed be unique among central nerve-mechanisms. As a matter of fact, the evidence against the views of Stewart and Rogoff on the function of the adrenal medulla has become overwhelming (17, 19).

In 1912 Elliott (27) found that reflex exhaustion of the residual adrenin of the glands was never obtained when the cord was transected above the origin of the splanchnic nerves, but that it could be realized when the brain-stem was divided just above the anterior corpora quadrigemina. He concluded that the reflex control of the adrenal glands is associated with the nerve-machinery in the neighborhood of the vasoconstrictor centre. Cannon and Rapport (23) found that the reflex secretion of adrenin is not impaired by a transection of the midbrain but is wholly abolished when the cut is just behind the inferior colliculi. They further showed that the increased discharge of adrenin incident to ordinary operative procedures is subject to inhibition by central vagal (depressor) stimulation and that the same transection which abolishes the augmentor reflex will put an end to this opposite reflex. A balanced effect can be produced by simultaneous elicitation of these opposed reflexes. One is strongly reminded of similar phenomena which Bayliss (6) obtained in his investigation of pressor and depressor reflexes; and taken together the results of these two lines of work afford additional evidence of the inseparability of sympathetic and adrenal mechanisms. Contributory evidence of a bulbar control of medulli-adrenal secretion was given by Carrasco-

Formiguera who reported (24) that piqûre will cause a discharge of adrenin into the blood.

Bulbar Control of Carbohydrate Mobilization

Following his great discovery of the glycogenolytic function of the liver, Bernard (8) concluded that it must be under the control of the nerves. He had come to regard that process as an internal secretion and so argued, that, like other secretions, it would be subject to the influence of a secretory nerve. Suspecting that the vagus was that nerve, but failing to obtain the expected result from direct vagal stimulation, he attempted to secure a more effective vagal discharge by irritation of the central origin of this nerve. His expectation was realized on puncturing the floor of the fourth ventricle (piqûre); a marked but temporary hyperglycemia with glycosuria resulted. Bernard's preconceived theory had borne fruit, but it turned out to be incorrect, as he himself soon discovered. Piqûre rendered the animal diabetic even with the vagi cut and he saw at once that they could not be the efferent nerves to the liver. Finally he found that the effect of sugar puncture was mediated by the spinal cord and the splanchnic nerves, which he recognized as sympathetic strands.

Although Bernard's experiments on sugar puncture gave proof of the possibility of a nerve-control of carbohydrate mobilization mediated by the sympathetic nerves (splanchnics), neither they nor similar experiments performed by later workers have served to localize a definite controlling centre (sugar centre). The bulbar area from which the effect can be produced is large and a similar temporary hyperglycemia can be produced by injury to many parts of the brain. Another method of approach is to investigate the possibility of inducing reflex rises in blood-sugar with various parts of the central nervous system excluded, but this has not been undertaken in any systematic way and until further data are available it is impossible to make a definite assertion that the bulbar region contains the reflex centre. At present it can only be said that since the floor of the fourth ventricle contains a central mechanism for the tonic and reflex excitation of many processes controlled by the sympathetic nerves, it is likely that there is a bulbar mechanism for the carbohydrate mobilization which can be induced by splanchnic discharge. The probability of this is strengthened by the fact that sugar puncture leads to a discharge of adrenin which, as many have shown, acts upon the liver to produce

hyperglycemia. Griffith's analysis (33) of the factors which produce reflex hyperglycemia has shown that the secretion of adrenin is as important as, if not more important than, the direct nervous discharge to the liver.

Other Bulbar and Spinal Sympathetic Mechanisms

There are certain processes under sympathetic control which have not yet been shown to possess any localized bulbospinal representation. These are secretion of sweat, erection of hair, inhibition of gastro-intestinal motility, pupillo-dilatation and a few other effects.

Sympathetic pupillo-dilatation, however, has received some attention in this connection. In 1851 Budge (11–13) and Waller (73, 74) were led to believe that the pupillo-dilator fibers of the cervical sympathetic nerve arise from the last two cervical and first two thoracic nerves. Budge described the corresponding segments of the cord as a "centrum cilio-spinale" and found that when this region is separated from the rest of the central nervous system, stimulation of any of its posterior roots caused a widening of the pupils. The result was probably due to a spread of current to the anterior roots. In the long controversy which followed Budge's work the bulk of evidence has been against the existence of such a centre. Anderson (1) obtained a slow dilatation reflexly from the isolated cord, but Karplus and Kreidl (47) could not produce this effect after cooling the upper segments of the cervical cord. The latter investigators admit that ocular reflexes, which are dependent upon the cervical sympathetic nerve, may be mediated through the medulla, but they regard the hypothalamus as the normal reflex centre for such changes.

A number of investigations have shown that the isolated spinal cord is capable of producing a sympathetic discharge to the sweat-glands. Luchsinger, who was one of the first to show that the sudorific nerves have a sympathetic origin, has demonstrated this fact (53); and recently Riddoch (36) has found that in men suffering from complete transection of the cord the slightest and most diverse sensory stimuli will induce profuse sweating from the regions of the skin innervated by the isolated part of the cord. This hyperhidrosis constitutes a part of the mass-reflex characteristic of these cases. Yet neither the results of the earlier worker nor those of Riddoch actually prove that the spinal cord is more than a conductor of sweat-impulses in the normal intact animal. With regard to the behavior of the iso-

lated cord in man, the mass-reflex is simply an indication that in the absence of the higher control spinal reflexes have suffered the loss of their local signature. The physiological state of such a cord is far removed from the normal.

The literature yields no good evidence for a bulbar sweat-centre, but cerebral control of this function is certain and that phase of the subject will be considered in a later section.

THE HIGHER CONTROL OF THE SYMPATHETIC NERVOUS SYSTEM

From what has been said in the preceding section it is apparent that bulbospinal mechanisms suffice for many tonic and reflex activities of the sympathetic nervous system. But it is possible that similar functions may be subserved by higher parts of the central nervous system and it is a fact that the lower mechanisms are influenced from above. It is therefore necessary to devote some attention to the nature of the higher control.

The Relation of the Cerebral Cortex to the Sympathetic Nervous System

As already stated the sympathetic nervous system has long been regarded as the connecting link by which the cerebral activities underlying emotional excitement act upon the viscera. In general it has been tacitly assumed that these activities occur at the highest level in the brain, namely, the cerebral cortex.

During the two decades which followed the discovery of cortical excitability by Fritsch and Hitzig in 1870 (30, 38), physiological literature was replete with reports of the localization in the cortex of almost every conceivable bodily function. Among the effects obtained during that orgy of cortical stimulation were those which are recognized as being under sympathetic control. Good accounts of this work are given by Schäfer (66) and by Ferrier (29). A study of the original reports has convinced the writer that many of the effects which were produced are to be accounted for on the basis of the spread of strong stimulating currents to subcortical regions or to the production of cortical epilepsy in which a widespread and unphysiological discharge occurs. The effects were rarely associated with stimulation of a single cortical area. Furthermore, in many instances, the animals were only curarized and in the absence of a true anesthetic there was ample opportunity for them to give reflex visceral responses to the

slightest dural or other purely afferent stimulation. When currents of weaker strength were used with light anesthesia a rise in arterial pressure was a common mode of response and in such cases it may be admitted that the result is attributable to a true cortical discharge. But it is significant that such results were obtained most commonly from the motor cortex or the immediately surrounding areas. They may be classed with those involuntary changes which accompany the performance of voluntary movements and which Bainbridge (4) has suggested result from an "irradiation" of pyramidal (voluntary) impulses upon bulbar centres. Widening of the pupils by cervical sympathetic discharge was one of the visceral changes most frequently reported by the early exploreres of the cortex, but more recently Parsons (59) has found that in the absence of the epileptic condition, it is only obtained from those cortical areas which are concerned in eye-movements. It is fair to apply to the earlier findings the criticism made by Ferrier (29) that "they are merely complications and not the results of localized cortical stimulation."

The method of cortical stimulation has most certainly failed to demonstrate a definite sympathetic representation in the cortex cerebri. There is no trustworthy evidence to show the existence of any cortical point of departure for impulses destined to reach the outlying sympathetic nerves.

Many who have sought evidence for a cortical control of the sympathetic nervous system have felt that the pronounced activity of that system during emotional excitement is to be explained on the basis of a cortical discharge. But it has been pointed out elsewhere (5) that while it is reasonable to suppose that the neural processes underlying emotional consciousness are indeed cortical, it does not follow that the bodily changes which make up emotional behavior are due to a nervous discharge of cortical origin. The behavior attending the major emotions, fear and rage, is primitive, energetically purposive and common to the various members of the mammalian order. Its occurrence is dependent upon the native inheritance of the animal and from the point of view of the physiologist an emotion is a typical reaction pattern (16). The behavior of an enraged cat is no more complex and no more the result of experience than are its postural and righting reflexes which have been so well described and analyzed by the late Professor Magnus of Utrecht (57). These considerations suggest that the reaction is dependent upon the older divisions of

the nervous system. There is much experimental evidence to show that this is actually the case.

When a dog or a cat is deprived of its cerebral hemispheres the capacity for the exhibition of emotional behavior is by no means abolished. After complete removal of all parts of the cerebral cortex except that of the basal part of the temporal lobe (which was disconnected from the rest of the brain) and with injury to the corpora striata and dorsal part of the thalamus, Goltz's dog (32) was kept alive for more than eighteen months. The general behavior of the animal has been frequently described and is well known. The dog's emotional activity was confined to a reaction, capable of regular elicitation, which closely resembled the picture of rage seen in a normal dog. The same was true of Rothmann's dog (65) which suffered ablation of the neopallium with partial injury of the olfactory cortex, corpora striata and dorsal parts of the thalamus, and lived in good health for three years before being sacrificed. Dusser de Barenne (26) has prepared and studied, in the chronic condition, two hemisphereless cats which showed marked emotional responses to various disturbances, innocuous as well as mildly harmful to them; merely lifting the animals caused energetic movements of defense and those reactions which are so characteristic of the angry cat—spitting, growling, and erection of the hair of the back and tail. The postmortem findings showed that in one of these animals the neopallium had been removed without injury to the paleocortex, archipallium or brain-stem and that in the other the ablation was comparable to that of Goltz's and Rothmann's animals. The trivial and often irrelevant nature of the conditions which would evoke the rage reaction in these four animals is noteworthy. It was induced in Goltz's dog by pinching the skin or by taking it from its cage, a procedure which invariably caused a violent protest, in spite of the fact that it was the usual sign for feeding and would have been quite agreeable to a normal dog. Snarling and growling were obtained in Rothmann's dog by a gentle scratching of the back, and the presence of a fly on the creature's nose sent it into a fit of rage. It is disappointing that in the observations of Goltz, Rothmann and Dusser de Barenne on the emotional behavior of their animals, only one sympathetic symptom is mentioned, namely, the erection of the hairs in the case of the cats. Other superficial signs of sympathetic discharge were undoubtedly present, but were evidently overlooked. Recently, through the kindness of Dr. Stanley

Cobb (67), the writer was afforded the opportunity of observing the behavior of a chronic decorticate cat which closely resembled the animals studied by Dusser de Barenne. This animal exhibited well-marked signs of anger, when disturbed. Pinching its tail not only caused hissing, with lowering of the head and arching of the back, but also erection of the hair of back and tail, distinct retraction of the nictitating membranes, dilatation of the pupils and separation of the lids (exophthalmos),—all signs of a sympathetic discharge.

The foregoing observations suggested to Cannon and Britton (18) the possibility of using an acute decorticate preparation for the study of the emotional activation of the sympathetic system. In acute experiments on cats they found that after disconnecting the cortex from the brain-stem there appears, upon removing the anesthetic, "a group of remarkable activities such as are usually associated with emotional excitement—a sort of sham rage." A prominent feature of this quasi-emotional state consists of signs of widespread activity of the sympathetic nerves; it is attended by the erection of hair, profuse sweating from the toe-pads, a high arterial pressure and discharge of adrenin from the adrenal medulla. Bulatao and Cannon (14) described the hyperglycemia associated with this activity and showed that medulli-adrenal secretion plays a major rôle in its production. Experiments which are being carried out at present by the writer indicate that the high heart-rates of this sham rage are produced by a direct sympathetic discharge to the heart by way of the accelerator nerves as well as by sympathetic activation of the adrenal medulla.

The observations on decorticate animals are consistent in showing that the removal of the hemispheres renders an animal unusually disposed to exhibit a behavior which is primitively emotional and comparable to that which enables the normal animal to meet the critical situations of life. They give strong support to the view that the nerve-mechanisms for the *expression* of rage are subcortical. They indicate that the rôle played by the cortex in the production of the bodily changes which accompany strong emotion is one which may actually involve a decrease rather than an increase in the influence exerted by the cortex upon subcortical mechanisms. The excessiveness and the easy elicitation of the rage reaction of decorticate animals gives it the appearance of a release phenomenon; and it is perhaps best explained on the basis of the view first advanced by Hughlings Jackson (43, 44) and more recently elaborated by Head (35)

to the effect that the cortex normally holds in check those activities of the lower and more archaic centres which would seriously interfere with its more discriminative reactions. The expression of emotional excitement is just this sort of activity and in the case of chronically decorticate animals release from cortical control must be the chief factor in producing the tendency to react excessively; there the chronicity of the behavior precludes its being the product of any sort of "irritation."

The Diencephalic Representation of the Sympathetic Nervous System

Some idea of the subcortical level responsible for the emotional activity of the decorticate animal can be gained from the results of experiments in which cerebral ablation has not been followed by such behavior. Both Woodworth and Sherrington (77), who worked with acute decerebrate cats, and Bazett and Penfield (7), who made a remarkable study of decerebrate animals in the chronic condition, have reported that with hemispheres, diencephalon and part of the mesencephalon removed certain pseudaffective reflexes may be elicited. It is, however, important to distinguish between the pseudaffective activity of these midbrain animals and the sham rage of decorticate animals. In the former, as exemplified by the experiments of Bazett and Penfield, the pseudaffective activity consists of isolated items of behavior and is typically brought forth by a stimulus ordinarily associated with some habitual mode of response. In the investigation made by Woodworth and Sherrington these reflexes were evoked by the strong stimulation of an afferent nerve and had a certain "width of co-ordination," but "they never amounted to an effective action of attack or escape." On the other hand the sham rage of the decorticate animal in the chronic (Goltz (32), Rothmann (65), Dusser de Barenne (26)) as well as in the acute (Cannon and Britton (18, 19, 21) Bard (5)) condition, is elicited by trifling disturbances of any kind, is astonishingly intense and possesses a width and energy of expression that makes it unmistakably the counterpart of intense fury in the normal animal. The central region which is responsible for this more general and more energetic affective behavior must lie below the cortex and above the lower half of the midbrain.

With these points in mind Bard (5) undertook an investigation directed toward the delimitation of the part of the brain-stem re-

sponsible for the sham rage of the decorticate cat. It was felt that not only would this elucidate the neural basis for this emotion but that it might advance the knowledge of the central representation of the sympathetic nervous system. The fact that it is in rage that the sympathetic system especially exhibits its tendency to discharge vigorously and as a whole, made it appear that the region sought represents a predominant, central, co-ordinating mechanism for the sympathetic system, a centre which when active will cause a discharge over the entire series of sympathetic preganglionic neurones. In a series of fifty-two successful experiments it was found that the sham rage occurs regularly after ablation of hemispheres, corpora striata and the cranial half of the diencephalon. But it invariably failed to develop when the brain-stem was transected at the caudal extremity of the diencephalon or through the cranial portion of the mesencephalon. That the part of the brain-stem necessary for the production of the decorticate rage lies ventrocaudally in the lower half of the diencephalon was indicated by experiments in which the typical activity developed after removal of the dorsal and cranial parts of the diencephalon. As a result of this investigation it becomes possible to state that the discharge of nerve-impulses which evokes the extraordinary motor activity of the decorticate preparation is conditioned by central mechanisms which lie within an area comprising the caudal half of the hypothalamus and the most ventral and most caudal fractions of the corresponding segment of the thalamus. The motor activities characteristic of the sham rage are both somatic and visceral. Struggling, snarling, clawing, and lashing of the tail are combined with erection of the hair, dilatation of the pupils, retraction of the nictitating membranes, exophthalmos, profuse sweating from the feet and enormous increments in arterial pressure and heart-rate. The last mentioned group of activities are due to a widespread discharge of sympathetic impulses and they are apparently occasioned by the activation of the same central mechanism which is responsible for the concomitant activity of skeletal muscle. These two aspects of the total activity are not separable and together form an integrated reaction.

The evidence for a diencephalic representation of the sympathetic nervous system which was obtained from a study of the decorticate rage is in accord with earlier physiological work. In 1909 Karplus and Kreidl (45) first found that in cats electrical stimulation of an hypothalamic point, lateral to the infundibulum, will produce maxi-

mal dilatation of the pupils, separation of the lids and retraction of the nictitating membranes. They showed that these ocular effects are mediated by the cervical sympathetic, that they are due to the stimulation of a true subcortical centre (46) and that no other parts of the diencephalon except the hypothalamus yield them (45, 46). They mentioned that in addition to the cervical sympathetic effects the stimulation induces profuse sweating from all four feet and, in subsequent papers (47–49), they have reported rises in arterial pressure. Houssay and Molinelli (39) have presented evidence to show that while weak electrical stimulation of the motor cortex, corona radiata, internal capsule and thalamus has no influence on the adrenal medulla, the same current strength applied to the hypothalamus is followed by a substantial secretion of adrenin. Schrottenbach (69) has studied the influence of the hypothalamic region upon the vasomotor responses of rabbits to psychic stimuli. He found that unilateral destruction of the hypothalamus temporarily abolishes normal rhythmic changes in ear-volume and the ability of the animals to respond to slight sensory disturbances (light, noises, cutaneous stimuli) by vasoconstriction of the ear-vessels.

Certain facts relating to the regulation of the body-temperature support the view that there is a diencephalic control of the sympathetic system. On the one hand it is established that the integrity of a region in the brain-stem lying above the middle of the mesencephalon and below the corpora striata is necessary for the maintenance of a constant body-temperature (7, 57, 64), and there is strong if not conclusive evidence that this heat-regulating centre is in the hypothalamus (41, 42). On the other hand, it is well known that erection of hair, ruffling of feathers, constriction of peripheral vessels, mobilization of sugar and increased medulli-adrenal secretion occur when the homothermic animal is exposed to a low environmental temperature. These activities are produced by sympathetic impulses and they have an important place among the bodily changes which resist a lowering of body-temperature. It is reasonable to suppose that this activation of the sympathetic nervous system has its immediate source in the diencephalon, for this part of the brain appears to contain the mechanism essential for temperature-control.

It is significant that exposure to cold and strong emotional excitement call forth similar bodily changes. Restlessness, trembling, shivering, and especially those visceral activities which denote a

widespread discharge of sympathetic nerve-impulses, are common to both conditions. Under both conditions these reactions represent an effort on the part of the animal to cope with a critical situation and they afford excellent examples of the emergency function of the sympathetic system. It now appears that in both instances they are dependent upon activity in the diencephalon. This suggests that the diencephalic representation of the sympathetic system constitutes that dominant central mechanism the existence of which is so plainly implied by the tendency of the sympathetic nerves to discharge vigorously and as a whole under conditions of stress.

The following sketch of the central representation of the sympathetic nervous system is suggested by the physiological evidence at hand. The preganglionic neurones which have their origins in the lateral horns of the thoracic and lumbar segments of the cord are normally under the control of supraspinal influences. This control may be exerted continually and so lead to a steady discharge of impulses to postganglionic neurones or it may become evident only when the controlling mechanism is set into action by circulatory, metabolic or reflex influences. The tonic discharge is subject to both central excitation and inhibition. Functionally similar groups of preganglionic fibers are normally under the control of their respective bulbar mechanisms, which suffice for the ordinary tonic and reflex sympathetic discharges. Higher levels are not essential for their activity. Superimposed upon these bulbospinal mechanisms is a dominant mechanism located at the base of the diencephalon and capable of causing a simultaneous discharge over the entire series of preganglionic neurones. The various functional activities of the sympathetic nervous system certainly appear to have a neural basis of this sort. The picture is still very hazy and it will require the close co-operation of the physiologist and of the anatomist to clear it.

DISCUSSION

The following questions submitted to Dr. Bard before the Commission, together with the answers to them, are here reported verbatim.

Dr. Huber: Mr. President, I shall probably propound questions a little later in the forenoon with reference to Dr. Bard's interesting paper.

I should now like to call attention to the fact that the medulla of the adrenal gland, while of ectodermal origin, is probably not of neuro-ectodermal origin. The

epiphysis and a portion of the hypophysis, as all of the chromaffin tissue, while of ectodermal origin are probably not a differentiation of the neuro-ectoderm but rather a differentiation of the ependymal and ectodermal supporting tissue of the central nervous system. Then, further, in the sham rage, there are in large measure involved somatic motor, efferent discharges. So far as concerns crying, breathing and movements of other body-muscle, I should think in terms of somatic motor discharge and not in terms of the sympathetic system. The ventral thalamus on the efferent side of the arc includes efferent subthalamic centres. The visceral efferent discharges have not as yet been definitely determined. The main discharge-path appears to be through the periventricular system and thence to the dorsal tegmental nucleus and through the fasciculus of Schultze to the bulbar centres.

I have been greatly interested in the work which Dr. Bard has done, not only as presented in this communication but also in former papers, linking up with the brilliant work in the physiological laboratory under Dr. Cannon's direction.

Dr. Cobb: Dr. Bard, I should like to ask if all of these experiments were acute experiments or if you had any that lasted over a long period? If the animal lived long enough to recover from the operative shock in any of these experiments?

Dr. Bard: In regard to Dr. Huber's statement, I agree with him entirely that one should not distinguish too sharply the sympathetic from the somatic activity of the sham rage, and I have said so elsewhere. On the other hand I think it is clear that there is a definite sympathetic representation in the base of the diencephalon. It is very difficult for me as a physiologist to visualize, in terms of morphology, exactly what happens in this region of the brain-stem during a fit of sham rage. The somatic activity is intense. The sympathetic activity is intense. The two cannot be separated. So far as I know, the part of the diencephalon which is responsible for the motor activity contains no somatic motor nucleus However, there is considerable evidence that there are present in the hypothalamus motor-nuclei which are in some manner connected with the preganglionic outflow of the thoracic and lumbar segments of the spinal cord. And Dr. Huber's own work is particularly interesting to me for the reason that it is a morphological study of the neural connections of this part of the brain. It gives some indication of the path of discharge of the impulses which evoke the peripheral activities.

In answer to Dr. Cobb's question, I may say that I have attempted to prepare a number of surviving decorticate cats after the manner of Dusser de Barenne, but with very poor success. They have lived, at the most, about eight days. They are extremely active and go to pieces rather readily. I will say this, however, that through the courtesy of Dr. Cobb I was able to observe, about a year and a half ago, a chronic decorticate cat which he had prepared with Dr. Schaltenbrand. They had removed the entire neopallium, and the cat lived in good health for some months before being sacrificed. Dr. Cobb allowed me to observe that animal on several occasions. It showed a marked tendency to react excessively to trivial stimuli. During such activity, which was quite similar to the sham rage I have just described, there was distinct evidence of widespread sympathetic activity.

This was indicated by a widening of the lids and dilatation of the pupils, a faster heart-rate, erection of the hair—all signs of sympathetic discharge. But so far I have not been able to prepare such an animal as Dr. Cobb's.

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CHAPTER V

THE FUNCTIONAL SIGNIFICANCE OF HISTOLOGICAL CHARACTER IN PREGANGLIONIC VISCERAL NEURONES[1]

EDWARD F. MALONE, M.D.

INTRODUCTION

THE following article is based upon a study of the distribution of various types of nerve-cells throughout the human central nervous system, a study which has been continuous over a period of twenty years. A consideration of minute histological differences in cell-type has been carefully avoided, and only those differences have been taken into account which can be clearly demonstrated and which are not materially affected by variations in technique or in the condition of the tissues. The function of nerve-cells, unlike that of nerve-fibers, cannot be studied directly, but one can study the differences between nerve-cells employed in different types of nervous reactions, and can note the constant histological features of nerve-cells which always occur in various nerve-mechanisms whose activities exhibit in common some well-marked feature. In making such a comparison between the character of reactions and the character of the nerve-cells employed, only clear and well-known differences in nervous reactions have been used; for instance, it has been profitable to compare histologically, various centres employed in reactions very susceptible to fatigue with various centres engaged in reactions which show a marked resistance to fatigue. In studying the relation between some specific histological feature of nerve-cells and some specific feature of nervous reactions the comparison should be made under varying conditions, with various combinations of all histological and functional features other than the single pair which is being studied. Although this method of investigation is limited to those centres whose exact connections are at present known it has at least made possible a beginning in the study of nerve-cell function.

[1] From The Department of Anatomy, University of Cincinnati.

THE RELATION OF FUNCTION TO THE SIZE, FORM AND INTERNAL STRUCTURE OF NEURONES

Function. The function of a neurone presents two aspects. It may be considered as the local activity which occurs within the limits of the neurone itself; this may be termed the immediate or intraneuronic function. The second aspect of function involves the neurone's connections, and this aspect of function offers two varieties; for the structures to which neurones are connected may be grouped according to their topographical distribution or else according to their intrinsic function. The function of a neurone thus involves not only its immediate or intraneuronic activity but also the neurone's topographical and specific functional relations to the entire organism. Every neurone type is a complex of histological and functional characters, and any single character may occur in other types of neurones. The general functional significance of any specific histological character may be determined by a study of all neurone types which exhibit the character in question, noting the features common to those reactions which employ such neurone types. Accordingly any consideration of the functional significance of the histological complex of preganglionic neurones must be based upon the significance of the individual histological characters of this neurone type, each one of these characters being studied in various types of neurones.

A neurone consists of two radically different portions, the cell-body with its dendrites and, secondly, the axone. The dendrites are merely extensions of the cell-body cytoplasm and should be distinguished from those processes which form the axis cylinders of sensory fibers in peripheral nerves. These peripheral sensory nerve-fibers exhibit the fundamental characters of all axones, and their conduction towards the cell-body depends exclusively upon the fact that normally the stimulus must of necessity act at their peripheral ends. The difference in the location of the stimulus in sensory and motor peripheral nerve-fibers is of great significance in relation to the entire organism, but it has no bearing upon the intrinsic activity of the nerve-fiber itself. While conduction can be directly studied in nerve-fibers it cannot be so studied within the other portion of the neurone, nor is there any ground for the assumption that within the dendrites and cell-body, conduction is of the same type as in nerve-fibers. Upon this assumption has been based the erroneous conclusion that

the peripheral type of conduction is maintained throughout the entire extent of any single neurone, and that the special features of conduction within the central gray matter depend exclusively upon the synapse. This incorrect conclusion is due partly to the lack of appreciation of the histological relations which may exist between two nerve-fibers. For as the nerve-impulse passes from the first nerve-fiber (axone) to the second, the region of transition may exhibit any one of three histological conditions. The two nerve-fibers may be directly continuous as in the typical peripheral sensory (unipolar) neurones, a condition which gains added significance from the fact that it is the result of the fusion of two originally separate nerve-fibers (axones). The second type of relation between nerve-fibers occurs in those bipolar neurones in which both processes are continued as nerve-fibers, as in the peripheral vestibular neurones; in this case the two nerve-fibers are separated by a cell-body without any synapse. In the third type the two nerve-fibers belong to separate neurones and are separated not only by the cell-body (and possibly by dendrites) of the second neurone but also by a synapse. Every synapse is followed by the cell-body of the second neurone; and since there is no proof that conduction is of the same type throughout the entire neurone, it follows that there is absolutely no basis for the assumption that the synapse only, and not the cell-body and dendrites also, is responsible for the special features which characterize conduction within the central gray matter.

Size. The study of various nerve-mechanisms, with reference to the size of the cell-body which each mechanism employs, reveals facts of interest. The size of the cell-body with its dendrites, is an indication of the extent of the neurone's activity, as well as of the frequency and duration of its stimulation; this involves the number of afferent connections and the extent to which these connections are employed. Neurones with large cell-bodies are employed continuously; those with small cell-bodies, intermittently. Moreover the size of the cell-body is an indication of its capacity to resist fatigue; nervous fatigue of central origin is not a function of the synapse but of the cytoplasm of the cell-body and dendrites. For in reactions which are continuous and not subject to early fatigue, such as the simpler proprioceptive reactions, not only the peripheral neurones but also the intermediate neurones have cell-bodies and dendrites in which the volume of cytoplasm is large. Whereas in exteroceptive reactions,

reactions of a more intermittent character and much more susceptible to fatigue, the cell-bodies and dendrites of the intermediate neurones have much less cytoplasm. Nor can the resistance to nervous fatigue be explained upon the basis of the use of neurones in rotation, for the small cell-bodies of the exteroceptive reception centres are more numerous than the large cell-bodies which constitute centres resistant to fatigue. Since the size of the cell-body and of the dendrites is an indication of the neurone's resistance to fatigue, it must also be an indication of its tendency to maintain a uniform irritability. Neurones with large cell-bodies are characteristic of centres employed in stable reactions, for the resistance to fatigue, the relatively uniform irritability and the relatively small numbers of cell-bodies in such centres all tend to direct the nerve-impulses into relatively fixed paths. On the other hand neurones with small cell-bodies characterize centres employed in labile reactions; the early fatigue, the variable irritability and the large number of cell-bodies all tend to produce a labile type of reaction, one in which the pattern is readily modified.

Form. While the size of the cell-body is related to the immediate or intrinsic activity of the neurone, the form is related to its connections with other structures. For in so far as cell-body form is of functional significance and not due merely to pressure it is determined exclusively by the number, size and form of the neurone's processes. Through its processes every neurone is employed in the collection and distribution of nerve-impulses. In afferent neurones the branching of the cell-body processes is as a rule such as to result in the predominance of the diffusing activity of the entire neurone, while in the efferent neurones the collecting capacity, with rare exceptions, is greatly in excess of the diffusing capacity. In both the afferent and efferent systems long distance transmission involves a decrease in the number and an increase in the size of the neurones. Due to the increased size of the cell-body, conduction is continuous, and its speed is greater, owing to the increased diameter of the nerve-fiber. Long distance transmission employs neurones whose collecting capacity is increased in relation to their diffusing capacity; in long efferent paths the neurones have great integrative capacity, while in long afferent paths the diffusion characteristic of afferent neurones is reduced in the interest of efficient transmission (resistance to fatigue, uniform irritability, increased speed and economy of the space occupied by the fiber-tract).

Either the collecting or the diffusing cell-body processes of the neurone may vary, not only in the number of connections, but also in the extent to which these connections differ topographically or functionally. Thus the central fiber of the peripheral neurones of common sensation is widely distributed to the primary sensory reception centres, whereas the termination of the medial lemniscus is restricted in area. The efferent system presents many instructive examples of variation of neurone form as related to the number and type of connections effected by the dendrites. The Purkinje cells of the cerebellum possess great collecting capacity due to the profuse branching of the dendrites, but these dendrites supply one continuous territory; in other words the collecting apparatus of the Purkinje cells is massive but of a low order of differentiation. In the inferior olives the cell-bodies receive impulses picked up within a narrow and almost continuous zone surrounding the cell-body; in this case the dendrites are numerous but small. Very different are the dendrites of the typical efferent neurones, such as the peripheral efferent neurones which supply skeletal muscle. In these neurones each of the dendrites constitutes a separate collecting system whose synapses are confined to a definite region relatively distant from the cell-body, each dendrite system supplying a definite region which is separated from the regions supplied by the other dendrites of the same neurone. Due to the separation of the fields of reception of each dendrite the neurone receives impulses from many different sources, impulses from different levels of the nervous system and from nerve-mechanisms of diverse functions. These typical motor neurones possess an integrative capacity of a higher order than that of the Purkinje cells, although the actual number of synapses may be less. Accordingly one must distinguish between the volume of impulses received by a neurone and the degree to which impulses arise from regions of the nervous system which are distinct; each of these two aspects of integration is, as just noted, related to a corresponding histological character of the dendrites of the neurone.

Internal structure. The internal structure of the neurone permits of an histological distinction between two functionally different portions: the axone which is resistant to fatigue, and the cell-body and dendrites which are subject to fatigue in inverse proportion to their volume. Moreover the internal structure of the neurone may be related to function in the arrangement of the Nissl substance, this

substance being arranged according to the integrative capacity of the neurone. A diffuse distribution is characteristic of afferent neurones, while in efferent neurones an increase of integrating capacity is accompanied by a concentration of the Nissl substance into granules of increasing discreteness. The sharply-defined, discrete character of the granules is related less to the volume of impulses received than it is to the capacity to integrate impulses from many diverse sources.

The foregoing discussion of the relation of function to the size, form and internal structure of neurones makes it possible to consider intelligently the functional significance of the complex of histological characters presented by preganglionic visceral neurones. The latter problem becomes relatively simple and may be disposed of briefly.

FUNCTIONAL AND HISTOLOGICAL SIGNIFICANCE

Histologically as well as functionally these neurones are efferent, but they resemble the more remote or premotor neurones rather than those of the peripheral somatic motor type. The latter, the typical motor neurones, constitute a well-defined group, differences being limited to size and to the number of impulses received, whereas the form and internal structure remain relatively constant as does the variety of source of the impulses received. The premotor neurones exhibit great differences in integrative capacity, the members differing not only in the size of the cell-body but also in its internal structure and in the nature of its dendrites. The cell-bodies and dendrites of some premotor neurones cannot with certainty be distinguished from those of neurones supplying skeletal muscle, but it is the less highly specialized premotor neurones which resemble the preganglionic neurones. Of all preganglionic neurones those whose cell-bodies constitute a portion of the dorsal vagus nucleus make the closest approach to the histological type of neurone which supplies skeletal muscle; but this resemblance is by no means perfect. These cell-bodies give rise to efferent vagus fibers which probably supply the heart; and they are of a histological type intermediate between that of the typical preganglionic neurones and of the typical motor neurones which directly supply skeletal muscle. Comparing these more highly specialized visceral neurones with the typical motor neurones it appears that the cell-body is smaller, the dendrites are less numerous, shorter and of decreased diameter, while the concentration of the Nissl substance into sharply circumscribed granules is less pronounced. The dendrites

of these preganglionic neurones are sufficiently numerous and of sufficient diameter and length to give to the cell-body a form which is still definitely polygonal. Comparison of these highly specialized visceral neurones with the usual type of preganglionic neurone reveals that the latter have smaller cell-bodies, that their dendrites are fewer, shorter and less massive, and that the cell-body has a less marked polygonal form. While the Nissl substance of the typical preganglionic neurones still has the general arrangement of all efferent neurones it is by no means characteristic, since the granules are relatively poorly circumscribed. If one compares the dendrites of the peripheral somatic efferent neurones, the dendrites of the large cell-bodies in the dorsal vagus nucleus, and finally those of the typical preganglionic cell-bodies, one finds that arranged in this order the dendrites diminish in number, diameter and length. As a consequence the neurones, taken in this order, receive stimuli which decrease in number and in variety of distinct sources; in other words, there is a progressive decrease in the integrative capacity of the neurone.

The preganglionic visceral neurones do not form a distinct group differing fundamentally from neurones of the somatic efferent system. The separation of the nervous system into visceral and somatic systems is incomplete, for both visceral and somatic responses may follow stimuli received from either system; and this separation is of necessity incomplete, since otherwise it would be impossible to integrate all the activities of the organism. The preganglionic visceral neurones must be grouped under the efferent neurones, their general histological character depending not upon their inclusion within the visceral system but upon the fact that these neurones are efferent or integrating. Their specific histological characteristics depend upon the extent of the demands for integration to which these neurones are subjected, and histologically their cell-bodies cannot be distinguished from those of somatic premotor neurones of corresponding integrating capacity. The cell-bodies of such premotor neurones occur, for instance, scattered throughout the exteroceptive reception centres and also in groups forming reflex centres along the central cochlear pathway. Such premotor neurones are employed only in very simple types of reactions, and histologically they indicate that they are subjected to relatively simple conditions, so far as integration is concerned.

CONCLUSIONS

The principal conclusions of this article may be summed up as follows:

The preganglionic visceral centres are merely reflex or co-ordinating centres of a low order.

The histological nature of these neurones does not depend fundamentally upon the fact that they belong to the visceral system, but upon the fact that visceral reactions are relatively simple.

The same histological character is shown by premotor neurones employed exclusively in somatic reactions of corresponding simplicity.

The histological nature of any neurone is determined not by the general function of the system to which it belongs but solely by the specific manner in which it is itself employed.

Histological differences in neurone types are quantitative rather than qualitative. In cell-bodies and dendrites histological differences correspond to quantitative differences in environment; differences in the number of sources of stimulation, in the extent to which these are used and in the extent to which these sources are differentiated into distinct fields of reception.

DISCUSSION

The following comment submitted to Dr. Malone before the Commission, is here reported verbatim.

Dr. Huber: Mr. Chairman, I have read this paper with great interest, but I have no particular question to ask the speaker.

I must confess to a little more optimism with reference to a determination of certain of the neurones under consideration. Certain of the visceral neurones after all mediate rather complex functional activities. If for example we think of the Edinger-Westphal nucleus and the adjacent somatic efferent nucleus of the third cranial nerve the two types of neurones are quite distinctive, although the visceral efferent Edinger-Westphal nucleus may have quite as complex functional activities as does the adjacent somatic efferent motor nucleus. It seems to me that the main thought of Dr. Malone's communication, —that not only the form of the neurones but the form and the connection must be considered in making division into types,—is quite true.

CHAPTER VI

DISTRIBUTION OF SYMPATHETIC AND DORSAL ROOT FIBERS THROUGH GRAY COMMUNICATING RAMI. ITS RELATION TO SYMPATHECTOMY AFFECTING THE EXTREMITIES[1]

ALBERT KUNTZ, M.D.

DISTRIBUTION OF WHITE AND GRAY COMMUNICATING RAMI

THE sympathetic nerve-fibers which are distributed to the peripheral blood-vessels, sweat-glands, muscles, and other sympathetically innervated tissues in the somatic area, arise in the ganglia of the sympathetic trunks and are conveyed to their peripheral destination mainly through the somatic rami of the spinal nerves. The ganglia of the sympathetic trunk are connected with the spinal nerves through the communicating rami. The latter include the visceral components of the spinal nerves which are functionally related to the sympathetic system, and the sympathetic fibers which join the spinal nerves to be conveyed to their peripheral destination. The spinal nerve components contained in the communicating rami are in the main myelinated and make up the white communicating rami; the sympathetic components are mainly unmyelinated and make up the gray communicating rami. Visceral components are absent in the cervical, lower three lumbar, and first sacral nerves; and the visceral components of the lower sacral nerves do not join the sympathetic trunk. Consequently, these nerves are connected with the sympathetic trunk only through the gray communicating rami. In general, the visceral components of the spinal nerves which pass through the sympathetic trunk are distributed to the internal organs. According to current teaching, neither preganglionic efferent nor visceral afferent fibers join the spinal nerves through the gray rami.

Sympathetic fibers are present in relatively large numbers in the somatic rami of all the spinal nerves. The cervical portion of the sympathetic trunk includes three ganglia, namely, the superior, middle,

[1] From the St. Louis University School of Medicine.

and inferior cervical sympathetic ganglia. The upper four cervical nerves receive gray rami directly from the superior cervical sympathetic ganglion. The middle cervical ganglion usually sends gray rami to the fifth and sixth, and sometimes also to the fourth and seventh cervical nerves. In the absence of this ganglion, these nerves receive gray rami from the inferior cervical ganglion or vertebral plexus. The inferior cervical ganglion sends gray rami to the seventh and eighth cervical, and usually also to the sixth cervical and first thoracic nerves. It also supplies fibers to the plexus on the vertebral artery. Fiber-bundles derived from this plexus join the lower cervical nerves, not infrequently as high as the fourth. Consequently, the vertebral rami of the inferior cervical sympathetic ganglion may be regarded as communicating rami.

The thoracic portion of the sympathetic trunk includes ten or eleven ganglia. In some instances the first thoracic ganglion, and rarely also the second, is fused with the inferior cervical to form the stellate ganglion. Each thoracic ganglion is connected with the corresponding spinal nerve by a white and a gray ramus which may exist as separate fiber-bundles or as a single mixed communicating ramus. When the white and gray rami remain anatomically distinct, the white ramus usually leaves the spinal nerve distal to the point at which the gray ramus joins it. Sometimes a sympathetic ganglion is connected with the spinal nerve by more than two rami. Occasionally a sympathetic ganglion is connected by communicating rami with more than one spinal nerve.

The lumbar portion of the sympathetic trunk usually includes four ganglia, but not infrequently more than four are present. Occasionally all the lumbar ganglia are more or less completely fused. This portion of the sympathetic trunk is connected with the upper two or three lumbar nerves by both white and gray rami, and with the lower lumbar nerves only by gray rami.

The sacral portion of the sympathetic trunk usually includes four small ganglia which diminish in size from above downwards. These ganglia are connected with the sacral and coccygeal nerves only by gray communicating rami.

INNERVATION OF PERIPHERAL VESSELS AND PERIARTERIAL SYMPATHECTOMY

The problem of the distribution of sympathetic fibers to the peripheral blood-vessels, especially the arteries of the extremities, has been

brought into the foreground anew by the surgical procedure now generally known as periarterial sympathectomy. The aim of this operation is to bring about the dilatation of the artery and its branches by cutting the nerve-fibers which run longitudinally in the adventitia.

The older anatomists, notably Goering (12) and Frey (10), were conversant with the fact that the peripheral arteries are joined by nerves along their course. According to Kramer and Todd (22), the subclavian and axillary arteries receive their nerve-supply directly from the sympathetic trunk, but all the other arteries of the upper extremity are supplied through rami of the spinal nerves, which join them at irregular intervals. The more distal vessels, particularly those of the hand, are connected by sympathetic filaments at shorter intervals than those in the proximal portion of the limb. The plexus on the abdominal aorta gives rise to a subordinate plexus on the common iliac artery, from which some fibers extend along the proximal portion of the femoral artery; but the more distal portions of the femoral artery and the other vessels of the lower extremity are supplied by sympathetic fibers which join them at irregular intervals through rami of the spinal nerves (Potts (44)).

The above findings were in general corroborated and extended by the studies of Hirsch (14, 15). His experiments show clearly that the number of rami joining the vessels of the extremities from adjacent nerves, is far greater, and that the total intrinsic nerve-supply of the vessels is richer than the results of the earlier studies seemed to indicate. In general, it may be stated that the vessels in the distal parts of both the upper and lower extremities are supplied by branches of the nerves which lie nearest to them. Although some fibers which join the axillary artery directly from the sympathetic trunk may extend distally along the proximal portion of the brachial artery, and some fibers derived from the plexus on the common iliac may extend distally along the proximal portion of the femoral artery, the anatomical data available at present do not warrant the conclusion that such fibers play any important part in the innervation of the vessels in the more distal parts of the extremities (Fig. 10).

In addition to their sympathetic innervation, the peripheral blood-vessels are also supplied by components of the dorsal nerve-roots. In a recent experimental investigation, carried out under the author's supervision, Kerper (19) isolated the sympathetic and dorsal root components of the nerve-supply to the arteries of the extremities in

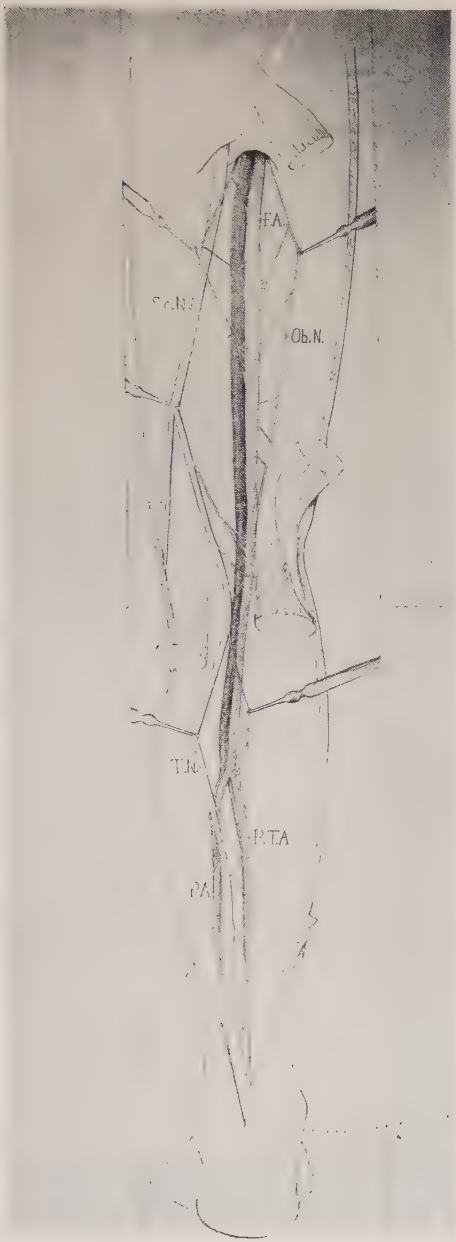

FIG. 10. Dissection of the lower extremity showing the distribution of nerves to the large arteries. *FA*, femoral artery; *ObN*, obturator nerve; *PA*, peroneal artery; *PTA*, posterior tibial artery; *ScN*, sciatic nerve; *TN*, tibial nerve.

the dog and studied each component separately, following the degeneration of the other. After the degeneration of the spinal nerve-fibers, following the section of both roots of the spinal nerves supplying the extremity just distal to the spinal ganglia, and leaving the sympathetic

Fig. 11. Tangential section of brachial artery of the dog after degeneration of the spinal nerve-fibers supplying the forelimb, due to section of both roots of the nerves of the brachial plexus just distal to the spinal ganglia. The sympathetic innervation is left intact. Unmyelinated nerve-fibers are indicated by black lines.

innervation intact, nerve-fibers remained intact in both the adventitia and media of the arteries; but the larger fibers normally present in the adventitia were absent. The number of nerve-fibers in this layer was appreciably diminished, but there was no apparent diminution in the number of nerve-fibers in the media (Fig. 11). Following the degenera-

tion of the sympathetic fibers, leaving the spinal nerve-roots intact, there remained a goodly number of nerve-fibers in the adventitia, and some in the media (Fig. 12). Those in the superficial layers of the adventitia were mainly myelinated; those in the deeper layers of the adventitia and the media were mainly unmyelinated. There is no reason to assume that somatic efferent fibers play any part in the

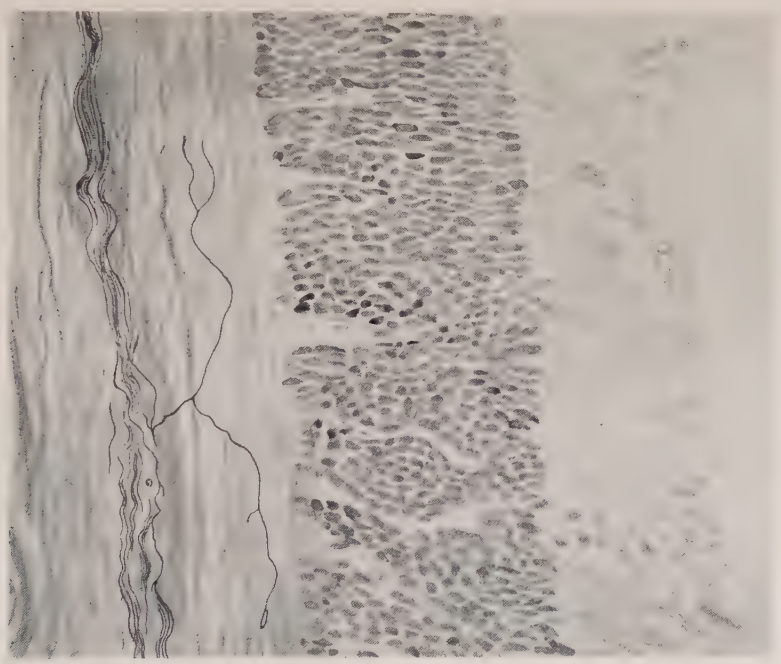

FIG. 12. Longitudinal section of the dorsalis pedis artery of the dog, showing dorsal root fibers in the adventitia after degeneration of the sympathetic nerve-supply to the limb, following extirpation of the lumbar and upper sacral portions of the sympathetic trunk.

innervation of blood-vessels; consequently, the fibers which remain intact in the vessel-walls, following the degeneration of the sympathetic supply, must be regarded as dorsal root fibers. The presence of sensory and end-organs in the adventitia indicates that at least some of these fibers are sensory in function. Whether any of them are parasympathetic could not be determined by the experimental

method employed. Kuré and others (32) recently reported the persistence of myelinated fibers of small caliber in the dorsal roots of the sixth and seventh lumbar nerves in the dog sixty-two and eighty-five days after the section of these roots proximal to the spinal ganglia. They interpreted these as efferent fibers which arise from cells located in the gray matter in the spinal cord, and probably terminate in relation to special nerve-cells in the spinal ganglia. In view of the negative results obtained by other investigators in repeated attempts to demonstrate the existence of efferent fibers in the dorsal nerve-roots, these findings can hardly be accepted without further confirmation. Their confirmation would render it highly probable that the dorsal root components distributed to the peripheral blood-vessels include parasympathetic fibers.

Following ligation and section of the brachial and femoral arteries and degeneration of the divided nerve-fibers in Kerper's experiments, the nerve-supply was greatly reduced just distal to the section, but was not appreciably altered in the more distal parts of these arteries. On the contrary, preparations of the femoral artery of an animal which had been subjected to section of the spinal nerve-roots and extirpation of the lumbar sympathetic trunk, were entirely devoid of nerve-fibers.

The above findings are in general corroborated by the results of Woollard's (53) study, by the use of similar experimental methods, of the innervation of the arteries in the hind-limb of the cat. They fully support the conclusion that the arteries of the extremities receive their nerve-supply mainly through vascular branches of the spinal nerves, and that the long fibers which extend peripherally along the brachial and femoral arteries play no important part in the innervation of the distal portions of these arteries and their branches.

In view of the anatomical relationships of the nerves supplying the peripheral arteries, it is clear that periarterial sympathetomy does not bring about denervation of the artery. Neither does it materially affect the peripheral vasomotor mechanism. Yet, in view of the favorable clinical results reported from this operation, there seems to be no reason to doubt that in certain cases in which the blood-supply to an extremity was diminished beforehand, periarterial sympathectomy resulted in a more or less permanent increase in the blood-supply of the extremity and in lasting benefit to the patient. Neither can it be denied that this operation was a factor in alleviating pain in some instances. On the other hand, the percentage of cases which were not benefited by periarterial sympathectomy, is relatively high.

Certain investigators, including Kappis (18), Seifert (50), Drevermann (9) and others, have maintained that the beneficial results observed after periarterial sympathectomy, are due to the hyperemia resulting from the partial sympathetic denervation of the artery. Others, including Läwen (35), Kümmell (25), W. Lehmann (37), and Polák (43), supported the theory that periarterial sympathectomy results in a change in the tonic condition of the entire sympathetic system by reason of the reflex stimulation of the sensory fibers supplying the artery. Still others (Kreuter (23, 24), Rieder (45, 46), E. P. Lehman (36)), supported the theory that hyperemia following periarterial sympathectomy, is the result of stimulation of short duration caused by the section of small fiber-bundles along the artery. None of these theories seems adequate to explain the hyperemia reported after periarterial sympathectomy. Neither can it be maintained that this operation is always followed by an increase in the blood-supply to the extremity. On the basis of the results obtained in experiments upon animals, Klug (21) denied the occurrence of an actual increase in the circulation through the extremity, following periarterial sympathectomy.

The alleviation of pain by periarterial sympathectomy is no less difficult of explanation, on the basis of the present knowledge of the innervation of the peripheral arteries, than is the production of hyperemia. Gundermann (13) supported the theory advanced by Leriche (38–42) that the alleviation of pain is the result of improved circulation and nutrition. Brüning (5, 6) and Drevermann (9) regarded it as a result of the absence of angiospasm. W. Lehmann (37) explained the alleviation of pain on the basis of the reflex inhibition of the vasoconstrictors resulting from the removal of centripetal stimuli from the artery, or from raising the threshold of stimulation of the sensory fibers supplying the artery, or from both these procedures.

Various investigators, notably Friedrich (11), Schilf and Stahl (49, 51), and Abrashanow (1), advanced experimental data in support of the theory that some sensory fibers run longitudinally in the periarterial plexus, and that the alleviation of pain by periarterial sympathectomy may be due to the section of these fibers. On the contrary, Dennig (7, 8), on the basis of his experimental findings, denied the existence of sensory fibers which run longitudinally in the periarterial plexus.

Although it cannot be denied that periarterial sympathectomy frequently results in some degree of peripheral vasodilatation, and that it has, in some cases, resulted in the alleviation of pain, it must be conceded that there is no rational anatomical or physiological basis for this operation as a clinical procedure. Neither do the results reported following periarterial sympathectomy, warrant its indiscriminate application.

SYMPATHETIC RAMI TO THE BRACHIAL PLEXUS, AND SYMPATHECTOMY AFFECTING THE UPPER EXTREMITY

In view of the anatomical relationships of the nerves supplying the peripheral blood-vessels, complete sympathetic denervation of the vessels of an extremity obviously requires either the section of all the gray rami through which the sympathetic fibers reach the nerves sending branches to the vessels, or else the extirpation of the corresponding portion of the sympathetic trunk. The section of the gray rami joining the lumbosacral plexus or the extirpation of the second, third and fourth lumbar ganglia, effectively removes the sympathetic innervation of the lower extremity. It has also been assumed that the section of the gray rami directly connected with the brachial plexus or the extirpation of the inferior cervical or stellate ganglion, brings about complete sympathetic denervation of the upper extremity. Clinical and experimental observations have shown, however, that these procedures do not in all cases completely eliminate the vasomotor nerves of the upper limb. This fact suggested the possibility that the inconstant intrathoracic ramus extending from the second to the first thoracic nerve, may constitute a pathway through which sympathetic fibers leaving the sympathetic trunk below the first thoracic segment, are conveyed to the brachial plexus. Accordingly, an investigation was undertaken to determine more accurately the frequency of this inconstant ramus in man and its relationship to the brachial plexus and the communicating rami which join the second thoracic nerve.

Although the second thoracic nerve gives rise to an intrathoracic ramus joining the first thoracic nerve in a large percentage of cases, it is not commonly regarded as contributory to the brachial plexus. According to the usual text-book statements regarding this inconstant ramus, it may join either the intercostal ramus of the first thoracic nerve or the brachial plexus only, or it may contribute fibers to both the first intercostal nerve and the brachial plexus. In forty-eight

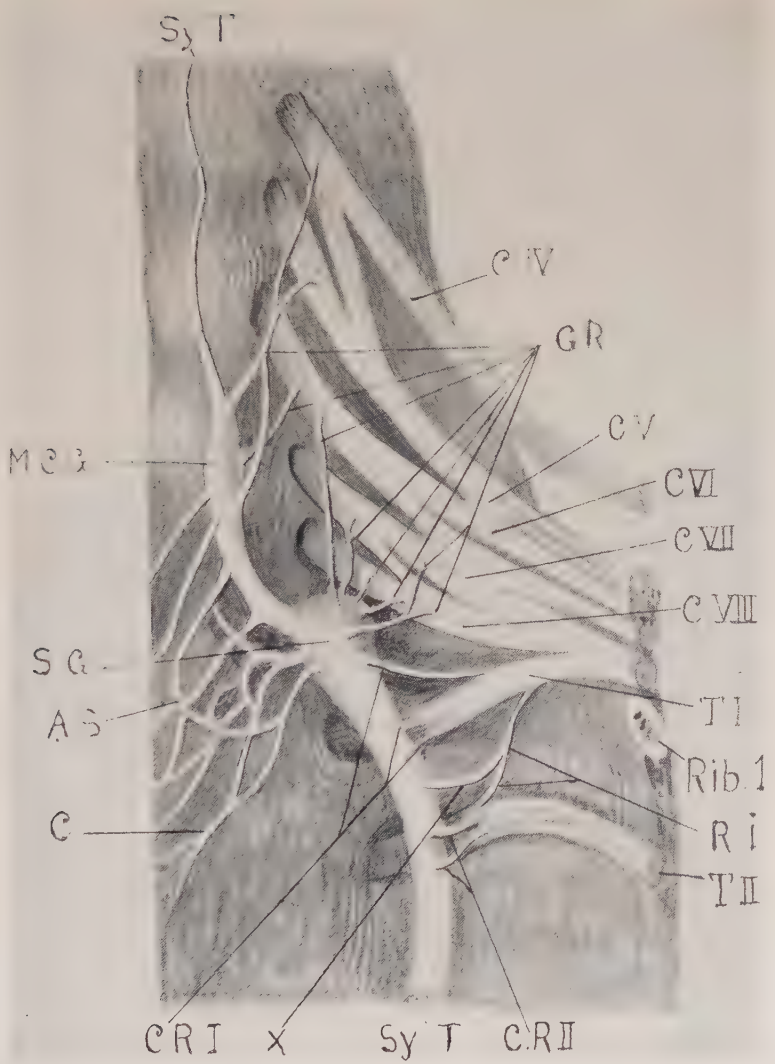

FIG. 13. Drawing from a cadaver illustrating the inconstant intrathoracic ramus from the second to the first thoracic nerve and the communicating rami joining the brachial plexus. *AS*, ansa subclavia; *C*, the cardiac nerves; *C IV* to *C VIII*, cervical nerves; *CR I*, communicating rami to first thoracic nerve; *CR II*, communicating rami to second thoracic nerve; *GR*, gray communicating rami to cervical nerves; *MCG*, middle cervical ganglion; *Ri*, inconstant intrathoracic ramus from second to first thoracic nerve; *SG*, stellate ganglion; *SyT*, sympathetic trunk; *X*, sympathetic ramus joining the ramus from the second to the first thoracic nerve; *T I*, first thoracic nerve; *T II*, second thoracic nerve.

cadavers examined in the author's study (Kuntz (26, 27)), an intrathoracic ramus connecting the first and second thoracic nerves was present bilaterally in twenty-one instances, and unilaterally in nine. In the twenty-one cases in which this ramus was present bilaterally, it was described as large in ten, medium in seven, and small in four. In the nine cases in which it was present only on one side, it was described as medium in five, and small in four. In all but six of the cadavers in which this ramus was present, it joined the first thoracic nerve proximal to the origin of the intercostal ramus of this nerve, thus constituting a pathway through which the components of the second thoracic nerve may enter the brachial plexus. Not infrequently this inconstant ramus of the second thoracic nerve is actually larger than the first intercostal nerve. In such instances, the second thoracic nerve clearly contributes fibers to the brachial plexus (Fig. 13).

The second thoracic nerve is commonly connected with the corresponding ganglion of the sympathetic trunk by a white and a gray ramus. In some instances an additional communicating ramus could be traced from the sympathetic trunk into the ramus connecting the first and second thoracic nerves. In such cases, one or more communicating rami also joined the second thoracic nerve. Not infrequently a communicating ramus joined the second thoracic nerve in close proximity to the point of origin of the inconstant ramus in question. Sometimes it was apparent that some of the fibers of the communicating ramus actually entered this ramus. In a few instances, a small ramus was traced from the second thoracic sympathetic ganglion directly into the first thoracic nerve.

Microscopic study of sections of the intrathoracic ramus connecting the first and second thoracic nerves taken at autopsy, revealed the existence in it of many unmyelinated and myelinated fibers of small caliber. A large percentage of the fibers of the gray communicating rami in these cases were also thinly myelinated. The same conditions were also found to exist in animals (cats and dogs) in which an intrathoracic ramus leading from the second to the first thoracic nerve was present. It may be assumed, on the basis of these results that the small myelinated and unmyelinated fibers in the ramus in question, are mainly sympathetic. Consequently, it may also be assumed that whenever this ramus joins the first thoracic nerve proximal to the origin of the intercostal ramus of the latter, it conveys sympathetic fibers to the brachial plexus. The distribution of these fibers in the upper extremity is not known, but available clinical and experimental

data indicate that at least some of them are distributed to blood-vessels.

In view of these findings, it is evident that complete sympathetic denervation of the upper extremity or its blood-vessels cannot be accomplished by the section of the gray rami joining the brachial plexus or by the extirpation of the inferior cervical ganglion alone, in any case in which an intrathoracic ramus of the second thoracic nerve joins the brachial plexus. Complete sympathetic denervation of the extremity would require the section of this ramus in addition to either of the above measures, or the extirpation of the upper thoracic portion of the sympathetic trunk, including the second thoracic ganglion.

This knowledge was applied recently by Adson and Brown (3)[2] in the surgical treatment of Raynaud's disease. They had previously attempted to relieve this condition in the upper extremity by the extirpation of the inferior cervical sympathetic ganglion and by cervical ramisection, but without success. In a case of Raynaud's disease in the upper extremities, they exposed the upper portion of the thoracic sympathetic trunk by a dorsal incision and resection of a segment of the dorsal portion of the second rib. They then divided the sympathetic trunk below the second thoracic ganglion, and removed a segment of the trunk, including the first and second thoracic ganglia. This operation, carried out first on the right side, resulted in the complete relief from the symptoms of Raynaud's disease in the right upper extremity. It was carried out later on the left side with complete relief from the symptoms in the left upper extremity. That complete sympathetic denervation of the upper extremity was accomplished by this operation, is indicated not only by the complete relief from angiospasm, but also by the absence of perspiration and the failure to produce perspiration in the upper extremities by the administration of sudorific drugs. It is also noteworthy that the ocular effects of this operation are less marked than are those of cervical sympathectomy.

SYMPATHETIC FIBERS IN THE MUSCULAR RAMI OF THE SPINAL NERVES

The sympathetic innervation of skeletal muscles cannot be discussed in the present paper except insofar as the anatomical data available indicate an unequal distribution of sympathetic fibers in the muscular

[2] See also this volume, pp. 721–765.

rami of the spinal nerves, and show that sympathectomy involving any somatic area results also in changes demonstrable by histological methods in the skeletal muscles affected.

Where preparations of the muscular rami of the spinal nerves have been examined following the degeneration of the dorsal and ventral root components (after section of the spinal nerve-roots distal to the spinal ganglion, but with the sympathetic innervation left intact, such as the vascular and cutaneous rami), numerous intact unmyelinated fibers have been revealed, although these fibers are not equally abundant in the rami supplying all the skeletal muscles (Kuntz (26, 27)). According to Kuré, Hatano, and others (30), sympathetic fibers are more abundant in the muscular rami supplying the muscles of the back, pectoralis major, gluteus maximus, quadriceps femoris, triceps brachii, and other muscles of the proximal division of the extremities than in those supplying the muscles of the distal divisions of the extremities, particularly the small muscles of the hands and feet.

Kuré, Hatano, and their co-workers (30) also reported the results of an extensive series of experiments involving the histological examination of muscles of the extremities at intervals following sympathetic denervation. They usually found no significant changes in the muscles soon after sympathectomy, but when the histological examination was carried out long (six to ten months) after sympathetic denervation, marked changes were apparent in most cases. In many instances, the majority of the muscle-fibers were atrophic and reduced in diameter, some of them being very slender. A few of the remaining fibers were described as hypervoluminous, while others had undergone no apparent change. The changes observed were not uniform throughout the cross-section of the muscle. In certain areas the majority of the fibers were reduced in size; in others, the majority were abnormally large; in still others, the majority were apparently normal. The interstitial connective tissue and the number of nuclei associated with the muscle-fibers were increased, especially in the areas in which the hypervoluminous muscle-fibers predominated. Neither were the changes equally marked in all the muscles examined. The large muscles of the upper arm and thigh were always more profoundly altered than the small muscles of the feet. Similar results of sympathetic and parasympathetic denervation were reported by Imagawa (16) in the muscles of the tongue, Sunaga (52) in the extrinsic muscles of the eye, and Sakarasawa (48) in the muscles of the face (Musculus

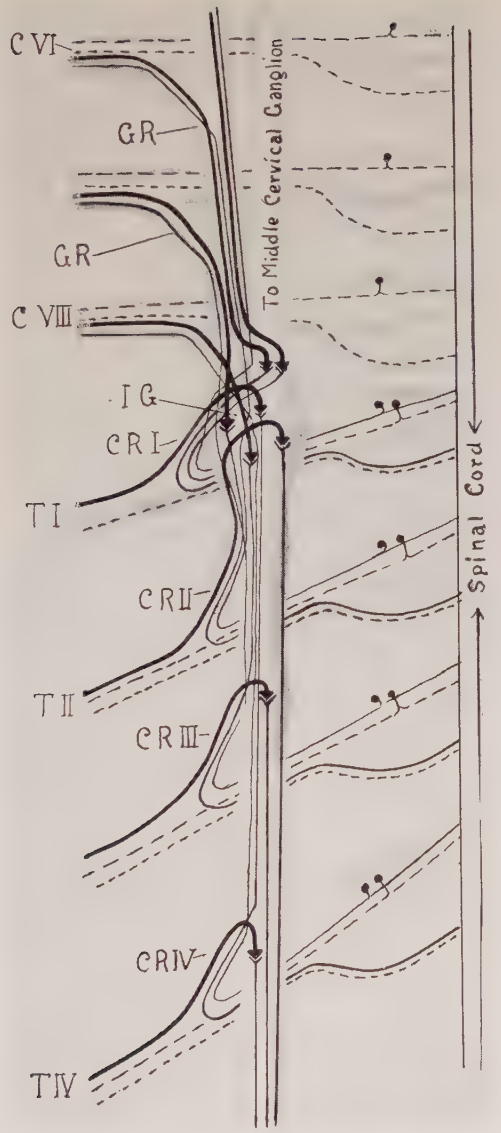

FIG. 14. Diagram illustrating the relationships of dorsal and ventral root components and postganglionic fibers to the sympathetic trunk and communicating rami in the lower cervical and upper thoracic segments. Broken lines represent somatic dorsal and ventral root fibers. Light solid lines represent dorsal and ventral root fibers which traverse the communicating rami. Heavy solid lines represent postganglionic fibers. *GR*, gray rami to brachial plexus; *IG*, inferior cervical ganglion; *CR*, communicating rami of upper thoracic nerves.

caninus and Musculus levator labii) in the dog. Atrophic changes which were comparable to those described in the muscles of animals under experiment, following sympathetic denervation, were also reported by Kuré, Tsuji, and Hatano (31) in the muscles of the face and neck in man, following cervical sympathectomy in the treatment of disease. Kuré (32) also pointed out that the muscular changes observed in clinical cases of progressive muscular dystrophy are similar to the changes observed in the muscles of animals under experiment, following the extirpation of the sympathetic nerves. They are also more marked in the muscles of the face, shoulder-girdle, arms, and thighs than in the more distal muscles, particularly the small muscles of the hands and feet.

In an investigation now in progress in these laboratories, Kerper (20) observed histological changes in some of the muscles of the fore-limb of the dog, particularly in the triceps brachii, two to three months after the extirpation of the stellate ganglion. These changes, in general, are similar to those described by Kuré and his associates, in muscles of the dog, but they are less marked. Kuré found many of the muscle-fibers reduced in diameter as compared with those of the normally innervated muscle. In general the myofibrillae were less compactly aggregated and less distinct in the atrophic than in the normal muscle-fibers. The cross striations remained distinct, but the sarcomeres were longer in the affected fibers than in those of the corresponding muscle on the unaffected side, although both muscles were removed and fixed under conditions as nearly as possible identical. The elongation of the sarcomeres, as determined by actual measurements carried out with the aid of the camera lucida, not infrequently approximated 20 to 25 per cent. Hypervoluminous muscle-fibers were less common in Kerper's material than in that described by the Japanese investigators. Hyperplasia of the interstitial tissue was also less marked. Kerper's material, however, was taken earlier, following sympathetic denervation, than that described by Kuré and his associates. Furthermore, as Kuré also pointed out, animals under experiment exhibit a relatively wide range of variation in the rate at which the observable atrophic changes take place in the muscles, following sympathetic denervation.

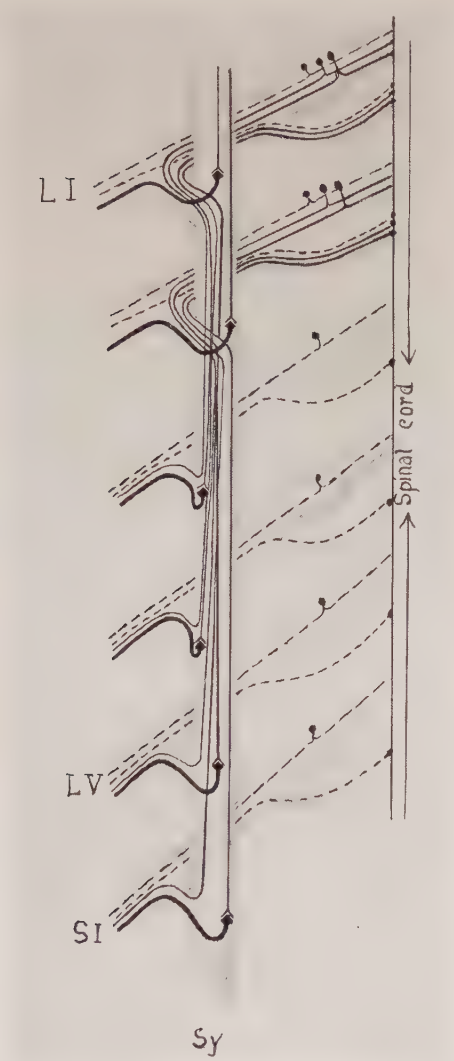

FIG. 15. Diagram illustrating the relationships of dorsal and ventral root components and postganglionic fibers to the sympathetic trunk and communicating rami in the lumbar and upper sacral segments. Broken lines represent somatic dorsal and ventral root fibers. Light solid lines represent dorsal and ventral root fibers which traverse the communicating rami. Heavy solid lines represent postganglionic fibers.

DISTRIBUTION OF DORSAL ROOT FIBERS THROUGH GRAY COMMUNICATING RAMI

Certain reflex phenomena were observed in animals, following partial denervation of a fore-limb (Kuntz and Kerper (29)) and the subsidence of pain, particularly in cases of thrombo-angiitis obliterans in the lower extremities, following lumbar sympathectomy (Brown (4), Adson (2)). These phenomena suggested the possibility that some afferent fibers which enter the sympathetic trunk through the white communicating rami may accompany the postganglionic fibers of the gray rami and may be conveyed to their peripheral destination through the somatic rami of the spinal nerves. The existence of some large myelinated fibers in the gray rami joining the brachial and lumbosacral plexuses, also suggested that these rami may convey, in addition to postganglionic fibers, some afferent components of the nerves through which the corresponding preganglionic fibers reach the sympathetic trunk. This would provide a means by which visceral afferent components of the upper thoracic and upper lumbar nerves could be distributed to the sympathetically innervated tissues of the upper and lower limbs, respectively.

Although Langley (33, 34) advanced certain data on the basis of which he concluded that some afferent fibers traverse gray rami to be distributed through the somatic rami of the spinal nerves, and that others traverse the gray rami to join the sympathetic trunk from nerves which have no white communicating rami, this view has not been generally accepted. The existence of afferent fibers in the gray communicating rami, except in cases in which the gray and white rami are not entirely separate, is not recognized in most of the more recent accounts. Johnson (17) reported the presence of large myelinated fibers in the gray rami of the sacral nerves in the cat and concluded, on the basis of his findings, that these were dorsal root components of the sacral nerves which joined the sympathetic trunk via the gray communicating rami.

In a recent study of the gray rami joining the brachial and lumbosacral plexuses in the dog (Kuntz and Farnsworth (28)) the following experiments were carried out. In one series of animals, both roots of the thoracic spinal nerves from the first to the eighth inclusive, were cut unilaterally just distal to the spinal ganglion, leaving the communicating ramus intact. In another series, some of the animals

were subjected to unilateral section of both roots of the lumbar nerves just distal to the spinal ganglia, from the first to the sixth inclusive; others were subjected to unilateral section of the sympathetic trunk just above the origin of the communicating ramus of the sixth lumbar nerve. The animals were killed from two to five weeks later. At this time the communicating rami joining the sixth, seventh and eighth cervical and the first thoracic nerves in the first series, and those joining the sixth and seventh lumbar and first sacral nerves in the second series, were removed bilaterally, fixed in osmic acid, and examined for myelinated fibers.

Osmic acid preparations of the normal gray rami in the dog, reveal a relatively small number of myelinated fibers. The great majority of the postganglionic fibers in the dog are unmyelinated. Consequently, this animal affords favorable material for an analytic study of the myelinated components of the gray rami. By actual counts of the myelinated fibers in cross-sections of corresponding gray rami, on both sides, following unilateral section of the spinal nerve-roots, the rami on the side of the operation were found to contain fewer myelinated fibers in every case than those on the unaffected side. The same condition also existed in the lower lumbar and in the upper sacral regions, following the unilateral section of the sympathetic trunk above the origin of the communicating ramus of the sixth lumbar nerve. The results in Table I are typical of those obtained in both series of animals.

Inasmuch as the preganglionic components of the efferent chains involved in the sympathetic innervation of tissues in the area of distribution of the somatic rami of the spinal nerves, make synaptic connections with postganglionic neurones in the ganglia of the sympathetic trunk, any fibers which traverse the gray rami, except those of sympathetic origin, must be regarded as dorsal root components. That they are fibers which join the spinal nerves via the gray rami, and not dorsal root components which join the sympathetic trunk through gray rami, is indicated by the fact that they undergo degeneration following the section of the nerves through which preganglionic fibers are conveyed to the sympathetic ganglia in question, although the spinal nerves joined by these particular gray rami remain intact. The myelinated fibers in the gray rami studied, vary in size within relatively wide limits. The number of large myelinated fibers in these rami is comparatively small. Following the section of the spinal

nerve-roots, nearly all the large myelinated fibers and a large percentage of the smaller ones undergo degeneration. The difference in the number of myelinated fibers observed in corresponding gray rami on the affected and unaffected sides in these experiments, may be regarded as the approximate number of myelinated dorsal root-fibers which traverse these rami. The dorsal nerve-roots, however, include many unmyelinated fibers which could not be differentiated from

TABLE I

MYELINATED FIBERS IN NORMAL GRAY RAMI IN THE DOG

DOG NO.	OPERATION	RAMI EXAMINED	NUMBER OF MYELINATED FIBERS	
			Left	Right
1	Both roots of upper 8 left thoracic nerves cut	Gray rami to 6th, 7th, and 8th cervical nerves	8	87
		Ramus to 1st thoracic nerve	15	166
		Total	23	253
9	Both roots of upper 10 left thoracic nerves cut	Gray rami to 6th, 7th, and 8th cervical nerves	25	184
13	Both roots of upper 6 left lumbar nerves cut	Ramus to 6th lumbar nerve	7	28
		Ramus to 7th lumbar nerve	0	18
		Ramus to 1st sacral nerve	0	8
		Total	7	54
14	Left sympathetic trunk cut just above origin of communicating ramus of 6th lumbar nerve	Ramus to 6th lumbar nerve	2	22
		Ramus to 7th lumbar nerve	0	7
		Ramus to 1st sacral nerve	0	0
		Total	2	29

unmyelinated sympathetic fibers by their microscopic appearance. Neither could degenerated unmyelinated fibers be detected in preparations of the gray rami by the method employed in the author's study of the subject. Consequently, the difference in the number of myelinated fibers in the corresponding gray rami on both sides, cannot be regarded as representing the total number of dorsal root-fibers in these rami. That unmyelinated dorsal root-fibers may also

traverse the gray rami joining the brachial and lumbosacral plexuses, seems not improbable.

CONCLUSIONS

The data available at present do not warrant the conclusion that any of the results produced in the extremities by sympathectomy are due to the interruption of the dorsal root fibers in the gray rami. As stated above, intact dorsal root fibers may be observed in the adventitia and media of the blood-vessels following the degeneration of the sympathetic fibers due to sympathectomy or to ramisection. Consequently, it cannot be assumed that the blood-vessels are wholly deprived of their afferent innervation when the dorsal root fibers which traverse the gray rami, are interrupted. Neither does sympathetic denervation alone deprive the other sympathetically innervated tissues of the extremities of all their dorsal root fibers. In view of these facts, the alleviation of pain in the extremities by sympathectomy cannot be explained on the basis of the interruption of the sensory fibers in the gray rami. Yet it is not inconceivable that the interruption of these fibers may be a factor in the alleviation of pain.

DISCUSSION

The following questions submitted to Dr. Kuntz before the Commission, together with the answers to them, are here reported verbatim.

Dr. Pollock: I have just one question I should like to ask Dr. Kuntz and that is whether it is not possible that the temporary results following periarterial sympathectomy, are due to a reflex activity motivated by the sensory impulses produced by injury to the vessel-wall.

Dr. Kuntz: That is the explanation that has been suggested by a number of investigators, and inasmuch as it is clear that the operation does not interfere materially with the distribution of fibers to the vessels, it is perhaps as good an explanation as we have.

Dr. Ferraro: I should like to ask Dr. Kuntz if he has been able to discover the origin of the efferent dorsal root fibers and to determine whether there are any cells in the ganglion which give origin to these fibers. I think that in 1922 by using the Golgi method, cells the prolongation of which enter the gray rami of the sympathetic chain, were described by O. Rossi (47). If this result is confirmed by further investigators, it may help in solving the problem of afferent stimuli through the sympathetic system.

Dr. Kuntz: I have no evidence of my own to support that theory. Of course, you are familiar with the work of the Japanese group, Ken Kuré and his associates (28–30), who claim to have demonstrated efferent fibers in the dorsal root of the lumbar spinal nerves. I do not know that they have actually demonstrated a special type of cell in the spinal ganglia, although they assume that there must be a special type of efferent cell in the spinal ganglia, and they assume that the efferent fibers which they could demonstrate in the dorsal root make a synaptic connection with those particular cells in the spinal ganglia which send their fibers out. Whether these are the fibers that go through the gray rami or not, is another question. Our anatomical investigations do not bear on this particular question. Perhaps Dr. Ranson can tell us more about that.

Dr. Ranson: Answering Dr. Kuntz's question, I would say that in my opinion Ken Kuré's results are not well established because he failed to exclude the possibility of the regeneration of fibers from the dorsal root. I feel sure that the majority of the fibers he saw are regenerated dorsal root fibers growing back toward the spinal cord.

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CHAPTER VII

THE INNERVATION OF THE MUSCLE-SPINDLE[1]

MARION HINES Ph.D.

INTRODUCTION

THE fusiform groups of small muscle-fibers separated by a connective-tissue enclosure from the surrounding skeletal muscle-fibers were first called spindles by Kühne in 1863 (42, 43). In all the forms so far investigated these fibers (Bremer (9)) are shorter and narrower than either the white or red muscle-fiber, but like the red they contain centrally placed nuclei and large myofibrils (Krause (41)). They are now known as intrafusal fibers (Sherrington (58)). The tissue capsule varies in thickness not only from phylum to phylum, but also from one species to another and further within different muscles of the same animal. In mammals Sherrington has (58) reported that an injection of the lymphatics of the limb in the cat filled the space between the intrafusal fibers and the investing connective tissue, the perilymphatic space. No such space has been described in birds, reptiles or tailless amphibians. These peculiar fusiform structures have not been found in either fish or tailed amphibians (Kerschner (38), Franqué (28), Giacomini (29), Baum (6)).

Certain mammalian muscle-spindles have been measured. They vary greatly in length and diameter, with age, with the animal studied and with the specific muscle in which they are found. In adult man, Baum (6) stated that they are 2 to 10 mm. in length, 0.08 to 0.25 mm. in width; Sherrington, for the ape and cat, 0.75 to 4 mm. by 0.08 to 0.25 mm.; Batten (5), for the dog, 3 to 4 mm. by 0.16 mm. The intrafusal fibers themselves in adult man were ascertained to be about 0.0135 mm. in width, or approximately one-third the diameter of the ordinary skeletal muscle-fiber (Christomanos and Strössner (14)). Cuajunco (21) found the intrafusal fiber in the adult pig to measure across its equator, 0.021, 0.012 and 0.008 mm., and the extrafusal fiber, 0.042 and 0.04 mm.

[1] From the Department of Anatomy, Johns Hopkins University.

The distribution of these organs (Regaud and Favre (55)) varies from muscle to muscle (Timofejew (66)) in the same animal. Speaking generally, they are more numerous in the muscles of the limbs than in those of the trunk, the head or the neck. They are more abundant in the muscles of the thorax than in those of the abdomen. Fränkel (27) found great numbers in the muscles of the thenar eminence in man; Onanoff (48), in the intrinsic muscles of the hand, the flexors of the fingers and the quadriceps femoris. But compared with these muscles they were rare in those of the trunk and rarer still in those of the abdominal wall. In certain muscles they are, apparently, entirely lacking. Sherrington (59, 60) did not find them in the orbital eye-muscles (see also Woollard (70)), the intrinsic muscles of the tongue and the diaphragm. On the contrary both Pilliet (51) and Langworthy (46) found them in the tongue musculature of the cat. Sutton (63) described what he thought to be a neuromuscular spindle in the extrinsic eye musculature of the developing pig. Cilimbaris (16) saw them in the extra-ocular muscles of the sheep, roe, stag, goat and wild pig, but could not discover them in the dog, cat, horse, rabbit, fox, hare, rat or domestic pig. It is possible that they are vestigial in the pig. They have never been described in the genital muscles, the cremasteric (Cavalié (13)), the ischiocavernosus or the bulbocavernosus (Baum (6)). Nor did Baum find them in the muscles of the external ear, in either of the bellies of the digastric, or in the laryngopharyngeus and the stylohyoideus. As definable organs they have never been observed in the facial muscles of the rabbit (Cipollone (17, 18)) nor in those of the fetal pig, the cat, the guinea-pig or the rat (Cushing Smith (62)). Cipollone, however, has found them in the external pterygoid and masseter muscles of the rabbit, and Cuajunco (20) has demonstrated them in the latter muscle of the fetal pig.

This review of the distribution of muscle-spindles uncovers little organization in their occurrence. Unless, perhaps, those muscles which develop in relation to visceral arches and have not since become attached to bone, do not possess these organs. However, it would seem that the greater are the diversity of use and range of activity to which the muscle is put, the greater the number of spindles found within it. The few muscles of the kitten studied by Hines and Tower (32) were characterized not only by the position of their contained spindles but also by the morphology of their nerve-endings. Such a

condition may account in no small way for some of the controversy of the later nineties over the exact morphology of various nerve-endings on the intrafusal fiber.

The nerve-terminations upon the intrafusal fiber are, with certain exceptions, concentrated in two places, around the equator and at one of the poles (Tello (64, 65)). That around the equator or middle point of the fiber is the continuation of a heavily medullated nerve-fiber. The polar ending comes off from a nerve-fiber which becomes non-medullated in the vicinity of the intrafusal fiber. The origin of the two sets of fibers and the variation of this general scheme form the subject of the present inquiry (Rauber (54), Trinchese (67)).

The spindles of frog-muscle have been described by Cajal (11), von Kölliker (40), Franqué (28), Huber and de Witt (36), Dogiel (22) and Sihler (61). All of these workers have found a medullated fiber which enters the equator of the spindle and ends as variously shaped projections from a longitudinal branching. Huber and de Witt mentioned that a non-medullated fiber penetrated the fine connective-tissue sheath about the equator of the spindle (Franqué), but could not tell whether or not that nerve-fiber played any part in the innervation of the intrafusal fiber itself. Cajal and Sihler both found a similarly placed medullated nerve-ending; and at one of the poles (or both, Cajal), quite outside the central enveloping connective-tissue sheath, a motor ending similar in morphology to that found on the large agranular muscle-fiber.

The muscle-spindles of snakes and lizards contain one intrafusal fiber; those of the vastus muscles of the tortoise as many as from two to eight. An accumulation of nuclei is found at the equator of the intrafusal fiber but no interruption of the cross striation. In addition to the usual sensory innervation at the equator, Ranvier (53) pictured another which he interpreted also as sensory, lying outside of the connective-tissue capsule. Perroncito (49) demonstrated a spiral ending around the central point of the spindle, while beyond, the intrafusal fiber received a non-medullated ending, a branch from a medullated fiber. The terminal of the other twig was a typical motor end-plate upon a striated muscle-fiber. In some instances, the polar ending originated from the medullated nerve-fiber in the immediate vicinity of the motor end-plate itself (Fig. 20). This appearance of a divided axis-cylinder would allow one to think of the second, or polar, ending as motor in character. The morphology of this ending varies from

that of a motor plaque to that of a typical *terminaison en grappe* of Tschiriew (68). Huber and de Witt pictured such endings in the tortoise as epilemmal but evidently saw nothing which resembled Perroncito's divided axis-cylinder. Nor did Kulchitsky (44) report such a finding for the innervation of the single intrafusal fiber of the python. In this reptile (Fig. 16), the heavy medullated fiber forms no spiral around the equator of the muscle-fiber but rather runs parallel to it, and the non-medullated fibers ending in *terminaisons en grappe* are distributed to the same intrafusal fiber within the outer limits of the extensions of the medullated fiber. The first, Kulchitsky believes to be somatic-sensory and the second, motor, originating from the sympathetic nervous system. Boeke (7) also considers that the spindle muscle-fibers of lizards are innervated by the sympathetic nervous system.

The literature evaluates differently the evidence for the origin of the motor innervation of the reptilian intrafusal fiber. Kulchitsky's guess and Boeke's statement may be correct, but it is difficult to discount Perroncito's (49) finding. A year later this investigator (50) added to his previous observation a non-medullated fiber, which entered the equator of the spindle and made contact with the intrafusal fiber. This discrepancy of interpretation may be due to the muscle used for study, to the difference between the technique of methylene-blue and gold-chloride, to the animal studied or to fact. The relationship of the central nervous system to the intrafusal fiber cannot be conjectured; it can be made known by the study of degeneration experiments.

The spindles within a pigeon's muscle may contain from two to six intrafusal fibers (Huber and de Witt (36)). A medullated fiber enters at the equator of the spindle and is distributed over the intrafusal fibers in a manner similar to Perroncito's description for lizards. The secondary ending or *terminaison en grappe*, considered by Giacomini (29) and by Cipollone (17) as a motor plaque, took its origin from a non-medullated nerve-fiber and accompanied the medullated fiber into the spindle. Huber and de Witt (36) evidently did not observe this particular ending, although they relate finding a non-medullated fiber within the connective-tissue capsule. They thought it sympathetic in origin but did not say that it had a definite termination on the intrafusal fiber itself. Should the fiber in question be proven to have its cell of origin in the sympathetic chain, the claim

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Figs. 16 20

of Hunter (37) and of Royle (56) for the loss of tone following removal of the sympathetic nerve to the wing of chickens and sea gulls would have a morphological basis.

The ending around the equator of the intrafusal fiber of mammals was early described as forming a spiral (von Kölliker (41)) and interpreted as in the case of the other phyla studied as sensory (Kerschner (38, 39)). Ruffini (57) studied the morphology of this nerve-terminal in the cat. He distinguished three types of spindles, those with complex terminations, those with intermediate, and those with simple. The first had not only a complicated primary or equatorial ending but two flower-like and two polar terminations as well, one at each end of the spindle (Fig. 18). The second type had but one flower-like or secondary equatorial and one polar terminal; while the simple variety supported only the primary equatorial and the polar ending. Ruffini thought that not only were the two types of equatorial terminations sensory, but the polar ending as well.

Dogiel (23) studied the Musculus transversus abdominalis of the rabbit (Fig. 17). He noted that the spiral endings were derived from heavily medullated fibers, but did not picture Ruffini's secondary flower-like terminals. These secondary endings were suggested by Huber (35), and Huber and de Witt (36) to be the result of poor impregnations. Further, Dogiel described the morphology of the polar termination as similar to the *terminaisons en grappe* of Tschiriew (68), and as proceeding from thinly medullated fibers. Besides

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Fig. 16. Muscle-spindle of the python, showing the ending of the medullated (thick) fiber, thought to be somatic-sensory, and the non-medullated (thin) which Kulchitsky interpreted as sympathetic. (Kulchitsky (44), Plate iv, Fig. 11.)

Fig. 17. Reproduction of a methylene-blue preparation of a muscle-spindle from the abdominal muscles of the rabbit, showing the spiral ending of Ruffini (57) and the *terminaisons en grappe* from a non-medullated fiber. (Dogiel (23), Taf. II, Fig. 14, iv, a.)

Fig. 18. Neuromuscular spindle (Type I) from adult cat, showing plate-like ending at both poles, the central primary spiral and secondary flower-like ending of Ruffini. (Taken from Plate ii, Fig. 1, (57)).

Fig. 19. Muscle-spindle from the Musculus interosseus digiti in the cat, stained by the Bielschowsky silver impregnation technique. The degenerated ending originates from C7; the intact ending arose from T1. (Agduhr (2), Fig. 6.)

Fig. 20. Muscle-fibers of the lizard showing two motor end-plates. From each arises a fiber ending as a *terminaison en grappe* on the muscle spindle. (Perroncito (50), Figs. 1 and 2.)

these two definite endings upon the intrafusal muscle, Dogiel found another nerve-fiber which entered the spindle proper, without determining whether or not it had a definite ending on the muscle-fiber itself. Agduhr (2–4) pictured a slender non-medullated fiber lying in the connective-tissue sheath of the spindle.

Cuajunco's (21) study of the development of the spindle in the pig demonstrated that the annulo-spiral and flower-wreath endings were most common and the plate-endings, rare. Besides there were fibers which he believed to be sympathetic. They formed anastomoses with the fibrils of nerves which later became medullated. At birth there were fine "nucleated" fibers which accompanied the larger medullated ones and formed ringlets connecting themselves with the medullated fibers. Further, these "nucleated" fibers approached the spindle in a separate group. These morphological appearances are facts which are highly suggestive not of collateral fibers from the dorsal root ganglion but rather from the sympathetic ganglionic chain.

The first reported attempt to study the termination-loss following ablation of the dorsal root ganglion was made by Onanoff (48). Although he was not certain that he had not injured the ventral root, nevertheless he found degeneration only of the equatorial ending. This communication evidently was unknown to Sherrington (58) four years later. For then Sherrington cut intradurally the dorsal roots proximal to the dorsal root ganglion and the ventral roots. The heavily medullated fibers to the spindle remained morphologically intact, but of course could not function. He could not determine, by the histological technique used, what happened to the finely medullated nerve-fiber. But peculiarly enough, Sherrington could ascertain no degenerative change in the intrafusal muscle-fiber after this operation nor even after he had removed as much as an inch of the sciatic nerve. This finding of no subsequent intrafusal atrophy is supported in an interesting reciprocal fashion by Morpurgo (47). He found that forced exercise, which increased appreciably the diameter of the skeletal muscle-fiber, affected no change in the intrafusal fiber of the spindle. Evidently the same functional relationship does not exist between the polar ending and the intrafusal fiber as between the motor end-plate and the skeletal muscle-fiber.

Agduhr's (2–4) study of the plurisegmentally innervated spindle in the cat (Fig. 19), fails to demonstrate that the nerve-ending pictured as sensory was such, because the whole nerve had been cut at its point

of exit from the foramina intervertebralia. The polar termination shares at least one characteristic with the sensory ending, its epilemmal position. Not until the recent work of Hinsey (33) was the sympathetic nervous system definitely excluded. When the sympathetic system was given complete autonomy, he could fine no nerve-terminations (using Ranson's (52) pyridine-silver technique) on the intrafusal fibers of the small muscles of the cat's foot. In the converse experiments, isolating, in turn, the equatorial ending and the polar plaque, he found upon examination that intactness of the dorsal root ganglion was necessary for the normal appearance of the sensory ending; and the ventral root, for the polar plaque. Boeke (7), in a review of the innervation of skeletal muscle, pictured a degenerating polar ending following upon ventral root section.

Neither in the work of Sherrington, nor in that of Agduhr, nor again of Boeke was the possibility of sympathetic innervation definitely excluded. But Hinsey, although he did not use the same muscle for his study of sympathetic autonomy as he did for that of the dorsal root ganglia or of the ventral root, reported that the intrafusal fiber was independent only of the vegetative nervous system.

METHOD OF PROCEDURE

In certain small muscles of the frog (*Rana pipiens*), the American alligator and the kitten, the spindles were studied intensively,—first, in the normal animal, and second, under well-defined experimental conditions. Conditions were so chosen that either the loss of certain forms of nerve-terminals might be noted or the ending in the process of degeneration could be determined. The time-bridge between the operation and the death of the animal was determined by the rapidity of the process of degeneration.

TECHNIQUE

The procedure followed in the three species was essentially the same. The animal was killed by ether; a cannula was pushed through a slit in the ventricle into the aorta and secured by a cord; through this the vascular system of the animal was perfused with a solution of 1:5000 methylene-blue in sodium chloride hypertonic for the animal. The skin and the fascia were immediately removed from the muscle to be studied and it was left exposed for a length of time determined for each species studied. The time allowed for the frog was two and a half hours; for the alligator, four to five; and for the kitten, from one-half to two hours, depending upon its age. Then a 5 per cent solution of ammonium molybdate was

run into the cannula. After the animal was perfused with the fixing fluid, it was left thirty minutes to three hours. The whole of the muscle was then removed, washed in cold distilled water and mounted in glycerine between two slides secured by rubber bands. This method of staining and mounting enables the student not only to see the endings themselves but to trace their relation to the main trunks of nerve-distribution within the muscle.

Two flat muscles of the frog were studied, the pectoralis abdominalis and the sartorius. The main nerve-trunks crossing these muscles are composed both of finely and heavily medullated nerve-fibers. Lying along the small blood-vessels and capillaries are fine non-medullated fibers, beady in appearance. These fibers leave the blood-vessels, course over the muscle-fibers, play in and out of the smaller trunks of the nerves and in some cases appear to join the motor end-plates. This junction may be a form of actual protoplasmic coalescence,—that is, the non-medullated fiber does not have a separate hypolemmal ending in the vicinity of the motor plate, as Boeke (7, 8) has described it in certain animals, but joins the longitudinal branching of the end-ramifications of the motor end-plate itself.

This type of non-medullated fiber also penetrates the spindle, often at the pole opposite to the one which the heavily medullated fiber has chosen. This penetration, on casual examination, is very like the description given by Huber and de Witt (36), and by Dogiel (24, 25). If followed more closely, however, this fiber may be seen to contribute to the smaller longitudinal ramifications of the nerve-ending upon the much prolonged equatorial plate. In the normal spindle it is not possible to separate, with that degree of certainty which is the aim of all investigators, the ramifications on the intrafusal fiber which originate from the non-medullated fiber, from those which arise from the medullated one.

Before its entrance into the spindle the medullated fiber is distinguished by several knob-like twirls or spherical enlargements of the axis-cylinder. They are confined more or less to a limited region proximal to the point where the bifurcation and longitudinal branching begin. Generally speaking, but one such medullated fiber enters the spindle-group of muscles at the innervation-site. However, in the pectoralis abdominalis, two such fibers have been seen. At no time has the writer observed in the sartorius a polar innervation in anyway resembling the description or figures of Cajal (11) and Shiler (61).

Nevertheless, in the pectoralis abdominalis of specimens of *Rana pipiens* which vary in no perceptible way from the family studied except in size, an ending reminiscent of the Cajal and Sihler description has been seen on a few intrafusal fibers. In fact, this ending may be found on the muscle-fibers of some of the spindles within this muscle and not on others; and the method of study allows a complete examination of the total content of the muscle and the possibility of following the intrafusal fiber throughout its whole length.

The muscle-spindle of the sartorius muscle in the frog is innervated by two nerve-fibers,—the one arises from a longitudinallly disposed medullated fiber (Fig. 21); the other, from a transversely distributed non-medullated fiber, which has often in its devious course run beside a small blood-vessel. But the same organ in the pectoralis abdominalis in some instances, not in all by any means, is innervated also by a non-medullated fiber which ends on the intrafusal fiber in a grape-like termination, unlike the typical motor end-plate of Cajal's description.

When the dorsal root ganglia (third and fourth nerves for the pectoralis abdominalis; ninth and tenth nerves for the sartorius) are injured or the nerve supplying the muscle is cut at its exit from the vertebral canal, the heavily medullated nerve-fiber to the muscle-spindle shows degeneration and the longitudinal ramifications, which came off the end-bulbs, disappear. That degeneration leaves some of the finer ramifications and the non-medullated fiber. When the abdominal sympathetic chain is removed and the sartorius stained a week later (Fig. 22), the fine non-medullated fibers have disappeared. No such fibers then connect along the blood-vessel and anastomose with the motor end-plates or enter the muscle-spindle, although they are easily visible in the normal sartorius of the opposite side. When the ventral roots of the third and fourth nerves are cut, the fine beady non-medullated fiber and the heavily medullated fiber to the muscle-spindle remain intact and all motor end-plates and *terminaisons en grappe* within the Musculus pectoralis abdominalis disappear.

In the sartorius it is clear that the muscle-spindle is innervated by a medullated fiber and a non-medullated fiber. The former degenerates when the dorsal root ganglion is injured, or when the whole nerve is cut; but it does not do so, when the ventral root is severed inside the vertebral canal, nor when the abdominal sympathetic chain is ablated. The non-medullated fiber is found lacking only after the

Figs. 21–24

removal of the abdominal sympathetic chain. Besides these systems, some of the spindles of the pectoralis abdominalis of certain frogs have a third or polar ending which disappears when the ventral root is cut. The presence of this ending in no way modifies the essential peculiarity of the mode of innervation of the equator of the intrafusal fiber itself, but would rather alter the interpretation of the nerve-mechanism involved in the functioning of the spindle.

The study of the innervation of this sensory organ in the skeletal muscle of the alligator is at the present writing only in its initial stages. As in other animals, the number of intrafusal fibers within a muscle-spindle is not constant even within the same muscle. They vary from two to four or five in the spindles studied so far. Nevertheless the nerve-terminals about the equator closely resemble one another in form. In the surface flexors on the thigh the equatorial ending is the continuation of a heavily medullated fiber which in the vicinity of the spindle often divides dichotomously, to innervate two intrafusal fibers. This first branch again divides, sending at least two flattened cords parallel with the length of the muscle. From this cord many excrescences arise and embrace the intrafusal fiber. Not far from this termination another is often seen, originating from a non-medullated fiber, apparently the motor ending (Fig. 23). This ending has been noted as being a typical large *terminaison en grappe*.

Fig. 21. Untouched photograph taken of a normal spindle found in the left Musculus sartorius of Frog No. 329. A single medullated axis-cylinder divides in such a manner that the intrafusal fiber receives two terminations at its equator.

Fig. 22. A muscle-spindle found in the right Musculus sartorius of Frog No. 329, from which the three right abdominal sympathetic ganglia had been removed, seven days before. The fine ramifications on the intrafusal fiber are no longer visible. Only a few of these end-processes are seen beyond the end-bulbs on the somatic sensory axis-cylinder.

Fig. 23. A muscle-spindle from the Musculus ambiens of the alligator. The equatorial ending is heavily stained with methylene-blue and spreads itself along upon the intrafusal fiber. The polar ending can be seen as a branch of a thread-like non-medullated fiber, which courses across the face of the muscle-fibers. Other branches from the same fiber end on the extrafusal fibers.

Fig. 24. A muscle-spindle from Musculus ischio-femoralis of the American alligator. The darkly staining fiber is the equatorial termination and springs from one axis-cylinder. The spindle lies above a large nerve-trunk. In the lower part of the photograph, two nerve-fibers pass over the intrafusal fibers, giving off a minute branch, the polar ending. This ending is not adequately shown in the photograph.

In one of the figures the nerve-trunk distributing motor endings to extrafusal fibers may be seen to flow over one pole of the spindle giving off a minute branch supplying the intrafusal fiber with a nerve-terminal (Fig. 24). No non-medullated fiber was seen to enter and to mingle with the "sensory" ending. In preparations in which both the dorsal root ganglion was removed and the ventral root severed, no sensory terminations remained, after sixteen days, upon the spindle. In those where the dorsal roots proximal to the ganglion and the ventral roots were cut, the motor end-plates to the extrafusal fiber were degenerated and the polar ending on the extrafusal fiber was nowhere to be seen.

However, the small adductor of the thigh, the Musculus ambiens, was not completely denervated by either of these operations. When the dorsal root ganglion was removed and the ventral root cut, the equator of the spindle was peculiarly enough only partially denervated, and the polar ending was completely lacking. But a small branch from the remaining equatorial termination passed beyond the spindle and ended on an extrafusal fiber. Such a finding clouds an otherwise clear picture. For it would appear that a part of the "sensory" equatorial ending might be motor or that the extrafusal fiber must receive a fiber of dorsal root origin. Further experimental ablations are necessary to clear up this point. One thing is certain, however, the spindle in the alligator is bisegmentally innervated, although the source of the nerve-fibers concerned is not known at the present writing.

The beady, non-medullated fibers which are found along the blood-vessels—typical vascular nerve-nets—have never been observed to leave their course to distribute themselves over the face of the muscle, as is so common in the frog.

At present the writer cannot substantiate, upon this alligator material, Kulchitsky's conjectures (44) for the python, nor Boeke's (7) for reptiles, that the non-medullated fiber, ending on the intrafusal muscle-fiber, originates from the sympathetic ganglion-chain. The origin for this nerve-ending resembles that of the polar ending in kittens.

In the writer's investigation (31) upon the innervation of the muscle-spindle in the kittens, four different muscles were studied,—the interossei, the abductor digiti quinti, the lumbricales, and the outer sheets of the pectoralis major. The nerve terminals upon intrafusal

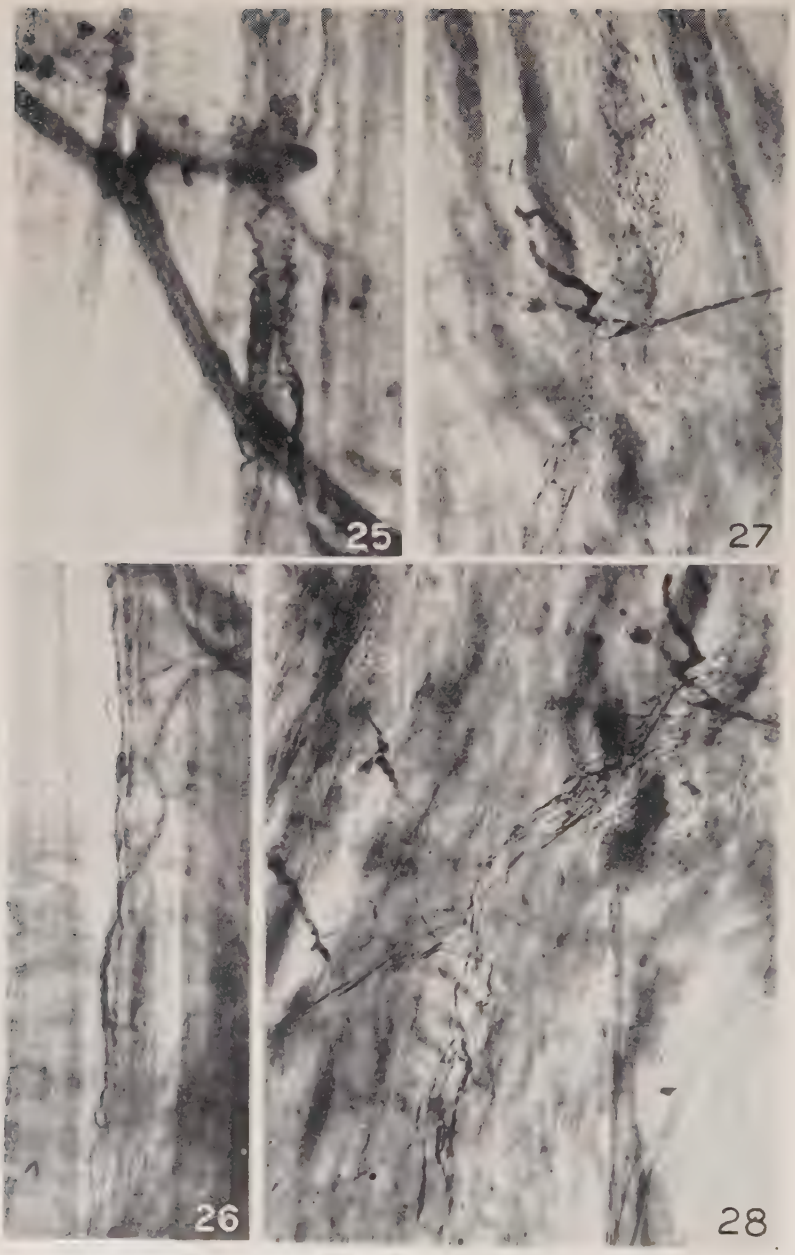
fibers within these muscles follow the common scheme, namely, an equatorial ending and a polar plaque. Yet a constant and peculiar morphology of the two nerve-terminations characterizes each of these muscles. Furthermore, the number and placing of the spindles within the particular muscle are rather constant.

The equatorial ending characteristic for the muscle-spindle of the pectoralis major is heavily medullated and forms a true spiral about the separate intrafusal fiber (Fig. 25). The polar ending is a single and diagrammatic *terminaison en grappe* coming off a slender, beaded, non-medullated nerve-fiber (Fig. 26). If, however, this non-medullated fiber, having the appearance of a typical "sympathetic" axis-cylinder, is followed backwards toward its source of distribution, it is found that this fiber becomes successively thinly medullated, then heavily medullated. This nerve-fiber does not share an axis-cylinder of origin with the motor end-plates of the extrafusal muscle-fiber.

The muscle-spindles of the interosseus muscles lie near the centre of their slightly swollen bellies. The equatorial ending shows not only a certain spiral tendency in its central portion, but also many incomplete semi-spiral excrescences, similar to Ruffini's (5–7) description of Type II spindles, but far more complicated (Fig. 27). The polar endings (Fig. 28) are not uniform in morphology or in relationship to the incoming fiber. They twist around the polar part of the intrafusal fiber, ending in close-fitting blebs upon it. The supplying nerve-fiber sometimes reaches the place of termination by entering from the side or running along the intrafusal fiber in a zigzag course. In the vicinity of its point of entrance this fiber always loses its myelin sheath.

The muscle-spindles of the abductor digiti quinti are quite similar to those of the interossei, although the extraspiral conformations of the equatorial ending are not as prominent. There are fewer intrafusal fibers in the spindle. The polar ending is simpler. It is innervated by a single nerve-fiber. In one of the muscles studied a single axis-cylinder was observed to divide dichotomously. One branch terminated as a complicated tendon-ending, the other, as the equatorial innervation of an intrafusal fiber (see also Weiss and Dutil (69)).

The same division of axis-cylinder and subsequent sharing of its branches between a tendon-like ending (Cattaneo (12), Ciacco (15), Golgi (30)) and the equator of a spindle was found also in the musculi



Figs. 25–28

lumbricales. The equatorial endings of these muscles have no definitely spiral portion; rather, they form small excrescences which ramify around the equator, not falling into any definite pattern (Fig. 32). The fiber which supplies the polar plaque leaves the trunk of nerve-distribution and ends directly as a *terminaison en grappe* on the intrafusal fiber (Fig. 33). Sometimes, however, a similar non-medullated fiber runs along the surface of the intrafusal fiber in a zigzag course.

It is evident from the description that the intimate details of the terminal morphology of nerve-muscle contacts upon the intrafusal fiber are typical for the four individual muscles studied. Nevertheless, in spite of this variation from the so-called normal pattern of nerve-endings within the muscle-spindle of the kitten there is no departure from the generalization that the equatorial ending is medullated at its point of contact and that the polar termination, non-medullated in the vicinity of its contact, originates from a medullated fiber. The question then arises as to the origins of these two fibers.

After the removal of the dorsal root ganglia which supply the muscle of the forefoot, the equatorial termination was either in the process of degeneration or completely absent, depending upon the length of time

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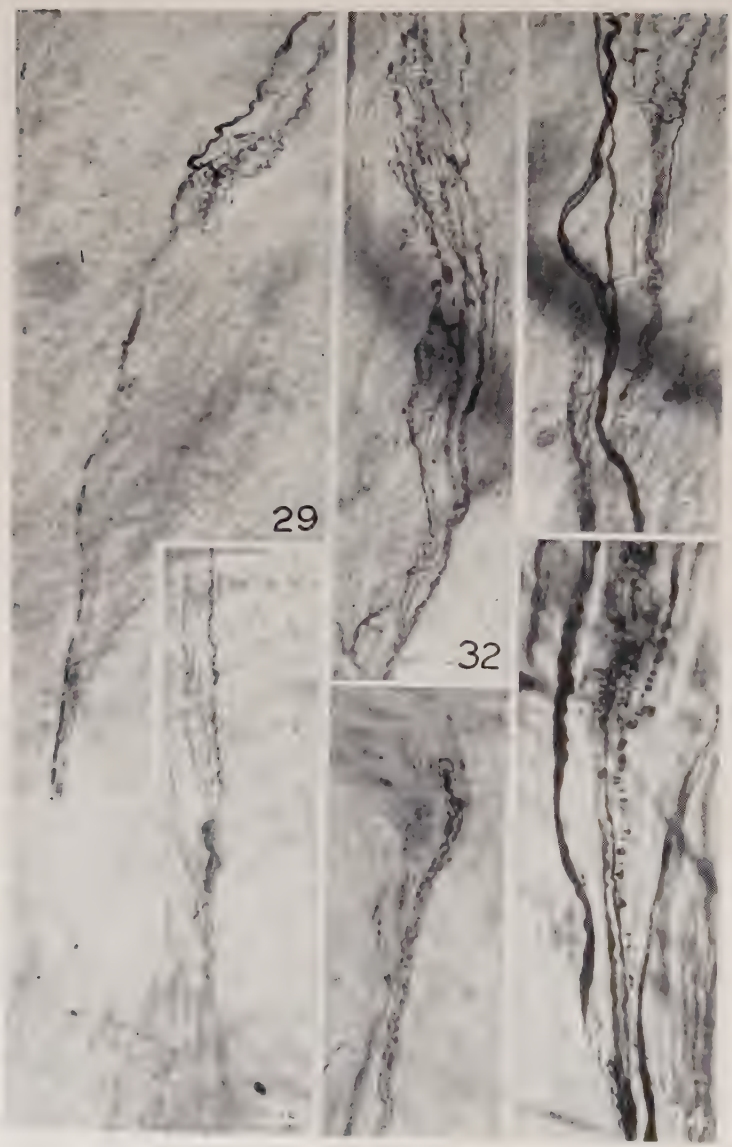
FIG. 25. An untouched photograph of a muscle-spindle, from the normal pectoralis major of a kitten. It shows the simple annular type of equatorial ending characteristic of the spindles in this muscle. The nerve-trunk may be seen giving off motor endings to the extrafusal fibers.

FIG. 26. The same spindle as that photographed in Figure 25. Two simple grape-like terminations can be seen, the polar innervation of the intrafusal fibers. The lowermost of these endings is the last branch from a medullated axis-cylinder before it became non-medullated. The non-medullated fiber courses out of the photograph and ends as a typical *terminaison en grappe* on an intrafusal fiber.

FIG. 27. This is an untouched photograph of the equatorial innervation of a muscle-spindle as seen in one of the interossei muscles of the right forepaw of Kitten V. R. I. Two nerve-fibers contribute to that innervation. The upper terminations are similar to the annulospiral endings described by Ruffini (57); the lower, to that of his flower-like terminals. A small blood-vessel filled with precipitated dye may be seen crossing the spindle.

FIG. 28. The same spindle as that photographed in Figure 27. The secondary equatorial ending lies above the polar ending. Two nerve-fibers contribute to the formation of the latter ending. Although they belong to the *terminaison en grappe* variety they are more complicated than those found in the pectoralis major. The morphology of these endings places this spindle between the complex and intermediate type of Ruffini (57), because no plaque was found at the opposite pole.



FIGS. 29-34

it was left after the operation (Fig. 31). The polar ending was altered (Fig. 30). When the ventral roots were cut and the dorsal root ganglia left intact, only the polar plaque showed evidence of disturbance. The equatorial nerve-terminal appeared normal (Fig. 29). Now if the anterior and posterior nerve-roots were severed within the vertebral canal distal to the dorsal root ganglia, and the ganglia removed, the whole innervation of the intrafusal fiber disappeared. In spite of its autonomy the sympathetic system did not demonstrate a part in the innervation of the spindle, although many nerve-fibers were found intact running along the blood-vessels.

When the stellate ganglion alone or the whole cervical sympathetic chain was removed, no débris of degeneration was found along the smaller blood-vessels whether the muscles were examined three days or two weeks after sympathectomy. However along the larger blood-vessels on the affected side, nerve-fibers were seen in process of degeneration. On this side, there was no sign of sensory loss in the muscles. There was no visible change in the appearance of the motor end-plates on the skeletal muscle-fiber, in the tendon-like endings,

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FIG. 29. The sensory termination on the intrafusal fiber is intact; the motor ending is seen as bits of broken and disintegrating axis-cylinder running parallel to the muscle-fiber of the spindle. This was taken from one of the interossei on the affected side of the forefoot (Kitten V. R. I), five days after extradural section of the ventral roots of C7 to T1.

FIG. 30. The intact efferent nerve running along the intrafusal fibers of a spindle was found in the affected interosseus muscle of the third digit of a kitten's forefoot, (D. R. G. IV). The dorsal root ganglia C7, C8 and T1, had been removed three days previously.

FIG. 31. A photograph of a degenerating nerve to the equatorial termination on the intrafusal fiber of a spindle, found in the left or affected Musculus interosseus quintus of a kitten (D. R. G. IV).

FIG. 32. The sensory termination on a muscle-spindle taken from one of the right Musculi lumbricales of Kitten Sym. II, three days after the removal of the right stellate ganglion.

FIG. 33. The motor ending upon the intrafusal fiber of a muscle-spindle from one of the right affected Musculi lumbricales (Kitten Sym. II). This remained intact, after the ablation of the right stellate ganglion.

FIG. 34. A spindle from the right or affected interosseus muscle of the middle toe of the forefoot (Kitten Sym. II). An intact equatorial ending, slightly out of focus, lies to the left of the spindle's penetrating arteriole. The small smooth muscle-cells in its wall take the methylene-blue stain. No nerve-fibers can be observed, coursing along this particular vessel.

nor any disturbance of the two terminations, characteristic of the intrafusal fiber (Figs. 32 and 33). The small arteriole, which in some instances supplies blood to the muscle-spindle, lost its accompanying non-medullated fiber after sympathectomy (Fig. 34). But this fiber was never found sharing the innervation of the penetrating vessel with the intrafusal fiber.

The results of these experimental degenerations allow no deviation from the generalization that the equatorial innervation has its cell of origin in the dorsal root ganglion and the polar plaque in the somatic motor column of the spinal cord. There is, therefore, nothing peculiar about the motor innervation of the intrafusal fiber in kittens. It is not sympathetic; it is, rather, similar in origin to that of the motor end-plate on the extrafusal fiber.

This method of examination of the whole muscle allows a study of the muscle-spindle *in situ* and enables a partial generalization that not only are the numbers of these spindles found within a given muscle approximately similar, but also that their position within the muscle approaches a constant and that each particular muscle is a type within itself. Further, the amount of connective-tissue encapsulation varies from muscle to muscle and within the same muscle. As many variations on the same simple theme were found in the equatorial ending as there were muscles studied. Generalizing from this small series, the greater the possible movement through space upon contraction, the simpler is the morphology of the equatorial ending; the finer the possible adjustment required in movement-sequence (as is the case in the intrinsic muscles of the paw), the more complicated is that termination.

On the other hand, there is but little variation in the morphology of the motor ending on the intrafusal fiber. The termination is a modification of the *terminaison en grappe* variety and never was found in this study to resemble morphologically the motor end-plate on the skeletal muscle-fiber.

The question still remains as to the significance for function of the variety of origin of the innervation of the muscle-spindle.

COMMENT

The knowledge of the central origin of the innervation of the muscle-spindle is fundamental for the construction of a plausible theory of its mode of functioning. There are two popular conjectures as to the

method of stimulation of this organ: first, by means of pressure-changes in the perifascicular sheath; and second, by the stretching of the whole muscle itself. According to the first, the contraction of the surrounding muscle is thought to lead to a change in the pressure of the so-called lymph inside the connective-tissue capsule. By the second, stretching is considered to stimulate the afferent fiber directly. As far as the writer knows, no direct experiment has been carried out to test the power of intrafusal or perifascicular pressure as an efficient stimulus. It is, rather, a theoretical deduction from the finding of Sherrington (58) that he was able to inject this intrafusal space through the lymphatics. Further, the tenet rests upon the anatomical description of a connective-tissue enclosure that appears rather tough. But this surrounding capsule is not a constant feature either in the studies made by the writer upon the frog, the alligator or the kitten; and what is more important, it is not constant in the different muscles of the latter. It is difficult to imagine pressure-changes in the negligible capsule of the frog's muscle-spindle as an effective stimulus, or for that matter in those of the kitten's pectoralis major. Such a difficulty certainly is not anatomically apparent in these organs as found in the musculi interossei, however. Either the effective stimulus varies from animal to animal or this theory of intrafusal pressure-changes will have to be abandoned, unless, of course it is experimentally proven.

Adrian (1) has demonstrated on analysis that the electrometer records taken from the nerve-trunk following the stretching of the sternocutaneous muscle of the frog are similar to those recorded by Forbes (26) for the sensory discharge from a contracting muscle. This similarity must be given due weight when the mode of stimulus of this end-organ is under consideration. Further, this similarity in the nature of the impulse set up in a nerve, following the activation of an intramuscular ending may be no more than a demonstration that whatever the type of activation, an impulse traveling toward the central nervous system has similar characteristics; for it is the similarity of the activity of the sensory nerve to that of the motor nerve stimulated artificially that has been used as the basis for the conclusion that the activity of the afferent and efferent nerve-fiber is of the same nature.

These explanations of the mode of activation of the sensory innervation to the spindle have, peculiarly enough, neglected the ex-

istence of the motor plaque upon the intrafusal fiber. In the three animals studied this termination, whatever its form, has a similar origin from the central nervous system. The neglect of consideration of this structure no doubt is due in part to Sherrington's report that the intrafusal fiber did not degenerate, as did its extrafusal cousin, when the spindle was isolated from central control, and in part, no doubt, because only within the past year has the exact origin of that nerve-fiber been known.

The motor innervation of the spindle does not allow it to be separated as a functioning entity from the motor innervation of the extrafusal fibers. If the ventral root is cut, it is logical to consider the possibility of the destruction of the reflex through the intrafusal fiber. In Coman's (19) beautiful study of the inability of the sympathetic nerve to maintain the tonic activity of the cat's forelimb when the ventral root was out, the efferent innervation to the intrafusal fiber was destroyed as well. If both the equatorial and polar endings must be intact for the normal functioning of the muscle-spindle, the possibility of the solution of the origin of the increase in tone characteristic of decerebrate rigidity from its reverse side vanishes. But if either the increase in intrafusal pressure or the stretching of the muscle be the effective stimulus for the spindle, then its functioning would indeed be independent of its efferent innervation. If this is so, the author is at a loss to account for the constant appearance of the motor plaque in the spindles of mammals and perhaps of certain reptiles. On the other hand, if the efferent nerve-fiber is responsible in part for the maintenance of a reflex through the intrafusal fiber, the question then arises as to why the intrafusal fiber does not degenerate when its efferent innervation is destroyed (Sherrington (58), Horsley (34)). To test either of these theories of stimulus as efficient for the intrafusal fiber is not impossible. They might be substantiated by cutting the ventral roots and modifying the intrafusal pressure (if the right muscles were chosen), or by cutting the ventral roots and subsequently putting the muscle under various degrees of tension; and in both procedures the subsequent passage of a nerve-impulse over the remaining intact afferent nerve-fibers in the partially degenerated nerve-trunk should be recorded.

Certainly, neither the increase of intrafusal pressure nor the intact somatic motor innervation to the spindle can account for its efficient functioning in the case of those organs in the frog's sartorius or for

those in the pectoralis abdominalis, on which no extra-equatorial termination could be demonstrated. The non-medullated fiber which Huber and de Witt (36) saw entering the muscle-spindles in the sartorius of the frog has its cell of origin in the abdominal sympathetic ganglia, and appears to take an active part in the formation of the ending around the equator of the intrafusal fiber. Strangely enough, when either the medullated fiber or the non-medullated fiber is destroyed the remaining ending does not appear as a clear-cut entity. When the sympathetic chain is ablated, the major part of the ending of the somatic sensory fiber disappears a short distance beyond its end-bulbs. When the other system is removed, the region of the equatorial terminations on the extrafusal fiber either stains diffusely or in minute spots, sometimes joined, totally unlike the uninjured spindles. Moreover, this region of the spindle is unaffected by cutting the ventral roots within the spinal canal.

The interpretation of this finding is difficult. There may be coalescence of the two to form the complicated ramification which is characteristic of the normal ending. However, it is not easy to believe that systems so diverse as the somatic afferent and the sympathetic efferent, could form a network such that when either is destroyed, the clearness of the other would be disturbed. It is not impossible that the metabolic products of degeneration of one system might effect a morphological change in the other; for such might account for the variability of the aspects of destruction following the experimental ablation of either system.

It will be remembered that occasionally in the Musculus pectoralis abdominalis of the larger variety of *Rana pipiens*, a polar termination was observed—a termination never similar in morphology to the motor end-plate as pictured by Cajal (11) but rather to that figured by Sihler (61). The presence of this extra-equatorial ending does not modify the peculiarity of the mode of innervation of the equator of the intrafusal fiber. It does, on the other hand, alter the interpretation of the nerve-mechanism involved in the functioning of the spindle. If Cajal's motor end-plates of somatic appearance, were found on all intrafusal fibers, it would place the frog's muscle-spindle in the same category with the innervation of the mammalian sensory organ, and it would then seem plausible to believe that here, as in mammalian muscle, the same impulse would cause a contraction of the ordinary skeletal muscle-fiber and of the intrafusal fiber. Such a contrac-

tion might in turn stimulate the somatic sensory ending. But the investigator is confronted with a sympathetic innervation.

If the sympathetic system represents, generally speaking, the only mode of efferent connection which the intrafusal fiber of certain muscles has with the central nervous system, such an explanation is difficult to believe, unless of course the central adjustor apparatus is as closely connected with the visceral efferent system as it is with the somatic.

The peculiar morphological changes in the frog's spindle which follow sympathetic ablation cause one to wonder whether or not Langelaan (45) may not have noted a certain atonia in frog's muscle. Unlike this organ of the frog's there is nothing in the alligator's or kitten's spindle from which to deduce a theory of loss of tone in sympathectomized muscles,—a finding which recent physiological work supports. It is not the explanation which Hunter (37) gave, but if the innervation of the goat's spindle resembled the frog's, it might explain his results. It may be remembered that Cuajunco (20, 21) found in those spindles of the pig which had a plaque-ending, an anastomosis between it and the fibers of the equatorial termination. Were the plaque-ending found to take its origin from the sympathetic ganglia, as he thinks possible, its ablation would undoubtedly disturb the clear-cut morphology of the equatorial ending. It is important to consider the subtle differences in the functional activity between the Musculus pectoralis abdominalis and the Musculus sartorius. It is possible that, anciently specialized as the frog has always been thought to be, phylogenetically speaking, it has not attained to that biological equilibrium expressed by the lack of individual variation in what has always been considered rather constant,—the relation of the peripheral nervous system to skeletal muscle.

The phylogenetic difference in the innervation of the intrafusal fiber might be correlated with certain differences found in the central nervous system. The increasing bulk and perhaps, therefore, the increasing importance of the fasciculi gracilis and cuneatus in the animals studied goes hand in hand with a greater complication in the peripheral terminations of the muscle-sense systems. The frog lacks entirely these dorsal columns. The central adjustor mechanisms on the afferent side for muscle-sense are the spinocerebellar tracts. A sympathetic efferent fiber, in close relation to the somatic afferent may be able to co-ordinate through the cerebellum in a more mechani-

cal manner than if the spindle were innervated from the somatic system.

The innervation of the spindle in the alligator is similar in relationship to the central nervous system to that found in the kitten, but the morphology of the terminations is apparently more constant from muscle to muscle. The reptiles are reported as possessing the beginnings of dorsal columns carrying proprioceptive sensibility. The nucleus gracilis is present, and there is some differentiation in the lateral group of nuclei belonging to the neothalamus. In the cat, these systems are rather well developed. The fineness of muscular adjustments in higher mammals and in man, particularly learned movements, are more dependent upon the dorsal columns than are those which have to do only with posture. This difference in the morphology and central origin of the spindles' innervation, between species and within diverse muscles of the same animal, may reflect a shift in the dominance of central systems concerned with muscle-sense (Byrnes (10)). It is a sad restraint upon the free play of imagination to have to conclude, that until shown otherwise, each species is a law unto itself and each muscle perhaps a particular case in some individual mammals, and that in order to make a true generalization about them, an infinite amount of further data will have to be gathered.

DISCUSSION

The following questions submitted to Dr. Hines before the Commission, together with the answers to them, are here reported verbatim.

Dr. Ranson: Dr. Hines is to be congratulated upon having secured such excellent preparations of the nerve-endings in the muscles with methylene-blue, a method which has enabled her to prepare a whole mount of a muscle and to examine it all, tracing the fibers for considerable distances. In spite of certain inherent difficulties and disadvantages in the methylene-blue method, this opportunity to study entire muscles is a great advantage; and her work, therefore, represents a very distinct addition to that which has been done with sections of muscles.

It seems rather remarkable to me that there should be such a marked difference between the frog and the mammal in the innervation of the muscle-spindle. This is a rather fundamental thing which we should expect to find alike throughout the vertebrates.

I should like to ask Dr. Hines what length of degeneration-time was allowed in her experiments upon the frog, and whether they were summer or winter frogs, because the degeneration-time varies with the season.

I should also like to ask whether I heard correctly that there is a possibility that the spindle has a sympathetic innervation in the cat? And whether Dr. Hines's observations have as yet been carried far enough to enable her to commit herself on the question of the sympathetic innervation of the muscle-fibers other than those within the muscle-spindle?

Dr. Hines: The degeneration-time in the frog certainly varies with the season. I have studied animals under experimental conditions in the fall, in the winter and in the spring. I find that the winter is not an advantageous season for such work because degeneration takes too long. Therefore, I work in the early fall and late spring. The particular picture which I showed was taken from the Musculus sartorius eight days after a complete unilateral ablation of the abdominal sympathetic chain, during the latter part of September. When one considers that not only is there a loss of these peculiar excrescences along the equator of the muscle-fiber within the spindle, but also that all the small non-medullated, beady-like nerve-fibers which lie along the smaller blood-vessels within the muscle itself also disappear, and, further, that these fibers which apparently (I only say "apparently") coalesce with the ordinary somatic motor end-plate of the extrafusal fiber of the frog are also gone, it at least seems reasonable to believe that I have demonstrated a loss in the equatorial termination of the intrafusal fiber of the frog.

In answering the second question, I may say that I have no evidence whatever that the intrafusal fiber of the muscle-spindle in the cat is innervated by the sympathetic system. When the sympathetic system is left intact and the other systems are allowed to degenerate, the endings on the interfusal fiber in the particular muscles that I studied are completely gone.

At the present time, I do not wish to commit myself in public on the question of whether or not the sympathetic system innervates the extrafusal muscle-fiber in the mammal, because it might get me into a great deal of trouble. About the condition in the frog, I am almost ready to publish what I have just said. I do not know what to say about the innervation of the extrafusal fiber of the alligator, because the last preparation which I studied, in which the central roots were definitely cut and the dorsal roots and the sympathetic left intact, I found within a single microscopic field a distribution of nerve-fibers which resembled morphologically every description that has been given up to the present time. In other words I found in some of these muscle-fibers a type of double innervation similar morphologically to that described for the python by Kulchitsky (44); in others, that similar to Boeke's (7, 8) description for the lizards he examined; and finally in others no trace of either of these varieties. Some of both the small and large muscle-fibers were innervated by medullated nerve-fibers. If I am able to substantiate this morphological interpretation by degeneration experiments, some of the present discrepancy will disappear. For mutually contradictory findings will exist and all investigators will be right, at least for the alligator.

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CHAPTER VIII

THREE TYPES OF FIBERS GOING TO SKELETAL MUSCLE AND ITS BLOOD-VESSELS[1]

JOSEPH C. HINSEY, Ph.D.

INTRODUCTION

IN MAKING any interpretation of physiological observations upon the skeletal muscles of mammals, it is of profound importance to know from the morphological side by what possible pathways nerve-impulses may travel in reaching the muscle-fibers. Investigators are divided in their opinions upon this matter and, generally speaking, one may say there are three schools of thought. Boeke believes that each skeletal muscle fiber is doubly innervated, by a somatic motor fiber and by a sympathetic fiber, either at the region of the motor end-plate or separated from it. The work of Kulchitsky suggests that, in skeletal muscle, there are two kinds of muscle-fibers proper, thick ones innervated by myelinated somatic motor fibers and thin ones supplied by non-myelinated thoracicolumbar sympathetic fibers. However, there are those who are not inclined to accept a double innervation of any kind for skeletal muscle, either because of the negative physiological findings, or because of a disinclination to accept the interpretations either of Boeke or of Kulchitsky.

The controversy over the double innervation of muscle-fibers from a morphological standpoint is a reflection of the difficulty of determining the origin of an unmyelinated fiber in the muscle itself. It is quite evident that there are three possible sources for unmyelinated fibers to the muscle: (*a*) the dorsal root component which, if one follows the teachings of Bell's law, should be entirely sensory; (*b*) the ventral root component which supplies the muscle with its somatic motor fibers; and (*c*) the sympathetic component whose function has been a matter of controversy in recent years. The literature covering this field has been reviewed recently by Hines (33) and by Hinsey (35), and it will therefore not be discussed in detail in the present paper.

[1] From the Institute of Neurology, Northwestern University Medical School, Chicago.

The fibers of the posterior root component have their cells of origin in the posterior root ganglion-cells having central branches which pass into the spinal cord and peripheral branches which pass out in the spinal nerve to reach the muscle. Sherrington (58) showed in osmic acid preparations that these fibers were of different sizes; the larger ones terminated in muscle- and tendon spindles and the small ones seemed to end after branching in free fibrils. Hinsey (35) used degeneration methods to isolate each of the three components of nerve-fibers to the skeletal muscle of the adult cat and stained them with the pyridine-silver method. He found fibers of many sizes of posterior root origin in the intramuscular nerve-twigs, the larger myelinated fibers supplying muscle-spindles, tendon-spindles and Pacinian corpuscles, and the smaller myelinated and unmyelinated fibers terminating in free endings in the adventitia of blood-vessels and in the perimysium and endomysium. Hines and Tower (34) employed similar degeneration methods and the methylene-blue stain with the kitten. They presented the variations in the form of the sensory endings in the muscle-spindles of different muscles, together with a study of the other sensory endings in the muscle. In one interosseus, they saw a sensory non-medullated axis-cylinder leave the main nerve-trunk, run along beside a small blood-vessel and turn into the connective tissue between muscle-fibers. They were led to the same conclusion reached by the author, namely, that "neither is the absence of a myelin sheath nor a brief course beside a blood-vessel, an adequate criterion of a sympathetic origin of an axis cylinder."

A review of the literature shows that skeletal muscle is supplied with a number of different kinds of receptors, among which are muscle- and tendon-spindles, Pacinian corpuscles, and free endings in connective tissue. Some of these receptors have probably differentiated in their phylogenetic development from more simple and less specialized endings found in the lower forms, such as the *terminaison en panier*, *terminaison en reticelle*, the grape-like terminations in the frog described by Kulchitsky (44), and unencapsulated tendon-endings as seen in the frog and reptiles. In some mammalian muscles, such as the eye- and tongue-muscles in some animals, differentiation into the highly specialized receptors probably has not proceeded as far as it has in some of the extremity and trunk-muscles. As a result there exist receptors of a more simple type, i.e., epilemmal endings from

both myelinated and unmyelinated fibers, as described by Huber (37), Crevatin (23-25), Dogiel (27), and Boeke (11). In classifying endings as being cerebrospinal or sympathetic in origin, it should be remembered that in certain muscles of some animals there are unmyelinated fibers of cerebrospinal origin, terminating in grape-like endings.

The ventral root component to skeletal muscle is made up of myelinated fibers whose cells of origin are in the anterior horn. As the ventral root component of the femoral nerve passes into the muscle, no unmyelinated fibers may be seen. These fibers in most cases remain myelinated until they reach their terminations, the motor end-plates. In some instances, however, the fibers become unmyelinated before they terminate. In preparations in which the posterior root and thoracicolumbar sympathetic components were removed and degenerated, the author has seen unmyelinated fibers leave the intramuscular nerve-twig to terminate in motor end-plates. In these cases where there was control of the degeneration procedures, he knew that these fibers had arisen from myelinated somatic motor-fibers. Without the isolation of the ventral root component, it would have been impossible to have said whether these endings were somatic motor or thoracicolumbar sympathetic.

During recent years in the physiological treatment of the muscle-spindles, it has been customary to ignore the previous literature which indicated that the muscle-spindle fibers themselves possessed a somatic motor innervation. This was undoubtedly due to the fact that the intrafusal fibers have not been shown to undergo marked atrophy after cutting the somatic motor supply. Boeke (15) shows an intrafusal fiber of a muscle-spindle of a cat after four days' degeneration following section of the spinal roots. Here the remains of a degenerating motor-plate are seen, while the annulospiral sensory ending is left intact. It is obvious that in order to prove the somatic motor innervation of the intrafusal muscle-fibers of muscle-spindles, it would be necessary to degenerate the posterior root component by total removal of the ganglia and the sympathetic component by excision of the sympathetic trunk. Then if any innervation remained, after sufficient degeneration time had been given the other two components, it would be somatic motor. After following this procedure, it was found that there was a somatic motor innervation for the intrafusal muscle-fibers. This observation was confirmed by Hines and Tower (34).

As soon as the muscle-spindles develop as specialized receptors, first in the anuran amphibians, the sensory and motor innervation appear, developing at the same time. The sensory endings serve as receptors, while impulses to the motor endings, by altering the length and tension of the spindle-fibers, probably make possible variations in the afferent stimuli received by the sensory endings. Furthermore, every time the spindle muscle-fiber reacts to an efferent stimulus, an action-potential wave is set up which might stimulate the sensory nerve-endings. The relation of the sensory endings to the spindle muscle-fibers would make possible such a stimulation.

Following the work of Hunter (39, 40) and of Royle (57) on the sympathetic innervation of skeletal muscle, attention was focused on the physiology of muscle-tonus. There is a preponderance of negative observations on the sympathetic control of muscle-tonus. Nevertheless, a structural relation between the sympathetic nervous system and skeletal muscle has been described and taken as proven by some authorities. Some workers have believed that the sympathetic nervous system exerts a trophic influence over the muscle-fiber and controls some of its physicochemical activities. However, it is difficult to put aside the vascular effects and eliminate them from a causal relationship in some of these observations. Before attempting to establish a functional relationship between the thoracicolumbar sympathetic system and the muscle-fibers, it would be important to know whether there really is an anatomical connection.

In gold-chloride preparations of lizard- and adder-muscle, Tschiriew (64) found grape-like terminations which he called *terminaisons en grappe*, supplied by unmyelinated fibers. He believed that they were cerebrospinal in origin. Bremer (19) described three kinds of fibers going to skeletal muscle in the frog and lizard: (*a*) large myelinated, (*b*) fine myelinated, and (*c*) unmyelinated. He believed that some of the unmyelinated fibers were sensory and some somatic motor. In another paper on the innervation of blood-vessels, Bremer (20) illustrates a branch from a blood-vessel going to a motor end-plate in the tongue of the frog. Sherrington (58) proved by degeneration experiments that all of the sympathetic fibers in the muscular and other peripheral nerves of the cat are unmyelinated. Huber and de Witt (38) and Dogiel (26) described vasomotor fibers in relation to the blood-vessels of the muscle-spindles but they did not describe any relationship of these sympathetic fibers to spindle muscle-fibers.

Grabower (32) used the gold-chloride method on human laryngeal muscle. The only unmyelinated fibers which he saw entering motor end-plates were branches of myelinated ones and these consequently fall into the category of collateral motor fibers. Perroncito (55) was in agreement with Grabower in thinking that the unmyelinated fibers which Bremer and Grabower had seen coursing in the sheath of Henle with myelinated fibers, were fibers which had divided from the myelinated ones. In addition to this type, Perroncito described another kind of unmyelinated fiber in the muscle of the lizard. These were unmyelinated as far as he could trace them, and they penetrated the motor plates to form a distinct intertwining. At first he thought these fibers were sensory but later believed they were ramifications of the sympathetic nerves.

In a series of rats, Floresco (29) resected the sympathetic cervical trunk. The rats were killed after twenty-four, forty-four, one hundred and twenty, and two hundred days. In microscopic sections of the masseter muscle on the side operated upon, there was no atrophy of muscle-fibers, no thickening of adventitia nor obliteration of the vessels. *Mastzellen* were not as numerous on the normal as on the affected side.

Gemelli (31) saw the endings which Perroncito believed to be sympathetic. Gemelli thought that they were ultraterminal fibers and not sympathetic in origin. In Golgi preparations of bird-muscle, Botezat (17) observed two types of nerve-fibers ending in skeletal muscle, both myelinated and unmyelinated. It is not clear from his illustrations whether or not all of the fibers which he showed are somatic motor, with unmyelinated fibers branching from the myelinated.

INNERVATION OF SKELETAL MUSCLE, ACCORDING TO BOEKE

In his earlier publication in 1909, Boeke (4) showed a series of drawings taken from the skeletal muscle of human and talpa embryos and from adult lacertian muscle. In these illustrations, he has shown unmyelinated fibers for which he has suggested a sympathetic origin and a possible tonic or trophic function. Later on in 1909, he (5) described more fully his accessory fibers. These were found easily in embryonic and young muscle and he found them also in the tongue of the adult field mouse, *Vespertilio*. However, his Figure 21 is unconvincing, inasmuch as the accessory plate here is probably only the plate of an ultraterminal fiber. He shows the accessory endings in the adult

lacertian muscle. In this paper the only illustrations which might be considered sympathetic are shown in embryonic and young muscle and in the adult *Lacerta agilis*.

In 1910, Boeke (6) answered the short paper of Botezat's (18) by pointing out that it is questionable whether Botezat had clearly shown the independence of the myelinated and unmyelinated fibers, entering the end-plates in birds. He shows only two figures of accessory fibers in young *Sturnus vulgaris*. His more complete work in 1911 (7) presents the form and structure of the motor end-plate of skeletal muscle in the higher vertebrates and, in addition, that of the accessory fibers and end-plates. He believed that, in addition to the epilemmal sensory endings, there are two kinds of hypolemmal endings, the usual motor end-plates of Kühne and the accessory endings. These latter are supplied by fine unmyelinated fibers which terminate in end-rings or nets. His observations led him to believe he was dealing with an independent system whose origin was in the sympathetic nervous system. One gains the impression from a study of his figures made from Bielschowsky preparations that accessory endings were present in embryonic and young animals and lacking in the adult mammalian muscle.

The author has not seen the original paper of Boeke's 1912 work (8) on degeneration of eye-muscle nerves in the cat, but he will describe it as presented in a later work (15). In cats, Boeke cut either the trochlear or the abducens close to its origin in the brain-stem. He allowed three and one-half to four days' degeneration time and found clumps of unmyelinated fibers which could be followed to hypolemmal accessory endings. Here he presented evidence which he believed would prove that skeletal muscle is innervated in two ways, each independent of the other. One of them, cerebrospinal motor, has myelinated fibers which terminate in ordinary motor end-plates. The other, the sympathetic accessory system, has unmyelinated fibers terminating hypolemmally in accessory endings.

A review of the literature dealing principally with the work of Perroncito and Gemelli is made in Boeke's 1913 paper (9). Here he tells of his inability to stain Perroncito-Gemelli fibers in preparations of lizard-muscle in which the motor end-plates and accessory fibers were successfully impregnated in gold-chloride, methylene-blue, and Bielschowsky material. He is inclined to think that there is a marked difference between them and his accessory fibers and he enumerates six differential points.

In a study of nerve-regeneration (10, 11), Boeke has described a series of degeneration experiments both on the eye and the tongue. On page 17 (11), the different series on the eye-muscles are outlined:

(*a*) In normal preparations, hypolemmal motor and epilemmal sensory nerve-endings are described from the extrinsic muscles of the eye of the cat. In addition to these are the small hypolemmal nerve-endings of unmyelinated fibers, the accessory fibers and endings.

(*b*) After cutting the eye-muscle nerves near their origin from the brain-stem and allowing a short degeneration time (three and one-half to four days), the motor and sensory endings are said to be completely degenerated and the accessory fibers and endings still remain intact.

(*c*) This series was similar to Series *b*, except that three weeks' degeneration time was given. The motor and sensory components were completely degenerated, and most of the accessory fibers and endings had disappeared. Boeke was able to observe unmyelinated fibers which had not degenerated in nearly all the nerve-branches between the muscle-fibers, page 18, "von welchen oft noch der Zusammenhand mit den Muskelfasern nach zuweisen ist, aber weniger klar als in den praeparaten der Serie *b*." These endings are not figured for this degeneration time, and evidently Boeke was not sure of their relationship to the muscle-fibers.

(*d*) The superior cervical sympathetic ganglion was removed and two weeks was allowed for degeneration of the sympathetic component to the eye-muscle. The motor end-plates and sensory endings were still intact as were the accessory fibers and their end-plates. However, he says, page 18, that one gains the impression that they are fewer in number than in the preparations of Series *a* and *b*.

In the same paper (11), Boeke outlines two series of experiments on the tongue of the hedgehog:

(*a*) After sectioning the lingual nerve on one side and allowing degeneration time (interval not given), he found a number of nerve-fibers present which branched in the connective tissue. These fibers formed a network which gave off here and there small end-nets which terminated sometimes very close to muscle-fibers in epilemmal endings. He believed that these fibers, which were similar to those Huber (37) and Dogiel (27) had described in the eye-muscles, ran in the hypoglossal nerve. Muscle-spindles have been described in the hedgehog tongue only in those muscles attached to the hyoid bone.

In Boeke's opinion, these epilemmal endings served to transmit muscle-sensibility.

(*b*) After cutting the hypoglossal nerve and allowing six days' degeneration time, he observed accessory fibers and endings on skeletal muscle-fibers. These endings resembled in every respect those described for the eye-muscles and other skeletal muscles, so he concludes, page 22, that in the tongue the accessory fibers which carry tonic impulses are independent of the hypoglossal nerve and run in the lingual nerve. He then brings out that these fibers may be the pathway for impulses in the pseudomotor phenomenon of Heidenhain. Two figures, 10 and 11, each show a very short unmyelinated fiber ending in the region of the degenerating remains of a motor end-plate. One is impressed with the shortness of these fibers in comparison with the length of the accessory fibers shown in the eye-muscles in the same plate.

In the tongue he did not find accessory fibers of thoracicolumbar origin but did find those of cranial origin. It seems rather heterodox to claim for autonomic fibers of the craniosacral division a function identical with those of the thoracicolumbar division, as it would be necessary to do in order to admit for the tongue-muscle an accessory sympathetic innervation similar to that which has been described in the intercostal muscle.

What at first sight appears to be the most crucial experiment in the entire series is that performed by Boeke in co-operation with Dusser de Barenne (16). They removed the posterior root ganglia and cut the ventral roots of T6, 7, 8, and 9 on the right side in a cat. Thirty days later, the cat was killed and autopsy showed that the posterior roots and anterior roots of these segments with the corresponding ganglia were cut through. Their report leaves some doubt as to whether or not the spinal ganglia were completely removed. Pieces of the intercostal muscles from the seventh intercostal space were cut out and stained after the method of Bielschowsky. The motor and sensory elements in the seventh intercostal space were found completely degenerated, while thin bundles of fine non-medullated fibers appeared to end hypolemmally by means of delicate end-organs, end-rings or end-loops or small end-nets. These end-organs are said to resemble in form the terminal ramifications of non-medullated fibers which remain intact in the eye-muscles after the stem of the eye-muscle nerves has been cut through. These results were interpreted to mean that the

muscles of the trunk have a sympathetic accessory innervation which carries efferent impulses.

In 1921, Boeke (12) described in connection with the endings of the accessory fibers a periterminal network which may be seen to surround both the ordinary motor end-plate branches and the accessory endings in the same plate. He assumes it to be the histological substratum for the receptive substance of the physiologists.

Boeke (13), after his observations on the *Tropidonotus natrix*, believed that reptilian muscle was supplied by two varieties of somatic motor fibers, those terminating in ordinary motor end-plates and those in *terminaisons en grappe*. He believed the latter to be hypolemmal. He observed a close similarity between the finer *terminaisons en grappe* and his accessory endings. He thought it very probable that some of the fine grape-like endings were supplied by sympathetic fibers which were said to occur in groups. However, the presence of sympathetic endings in this reptilian muscle is far from proven. This paper is interesting mainly because it gives the *terminaisons en grappe* a hypolemmal position and in most cases a cerebrospinal motor function. It will be seen that Kulchitsky presented another interpretation.

In a short paper in 1926, Boeke (14) replied to the criticisms of Del Rio Hortega and to Cajal. The latter (21) believed that the histological demonstration of accessory sympathetic fibers is very difficult, since it is impossible to distinguish with certitude an unmyelinated collateral, arising at some distance back from a myelinated motor fiber, from a purely sympathetic one. Cajal described here in the tongue-muscles of a young mouse, terminal motor plates with a large number of terminal accessory plates, formed by collaterals of motor fibers. He believed these collateral fibers and their endings served to confuse, inasmuch as they were similar to Boeke's accessory fibers and endings. Boeke replied by citing the degeneration experiments which had been done by Dusser de Barenne and himself, Kuntz and Kerper, and Agduhr.

Boeke's 1927 paper (15) contains a complete review of his entire conception of the innervation of skeletal muscle. In discussing his eye-muscle experiments, he says that he re-examined the material from his previous investigation and performed some additional experiments with longer and shorter degeneration times. He confirmed his earlier findings with the exception that he found a larger

number of accessory endings of thoracicolumbar sympathetic origin. However, attention should be called to the fact that the degeneration intervals of the new experiments are not stated and the endings are not figured. It is to be regretted that all of the illustrations are taken from three and one-half days' degeneration material instead of from longer intervals in the eye-muscle experiments. In his Figures 15, 16, 17, and 18 of normal eye-muscles, he does not state whether the material is young or old.

In refuting the conception of Hunter (39, 40) that the muscle-spindles contained fibers rich in protoplasm which received only sympathetic innervation, Boeke brought out the following points: (*a*) The motor end-plates of muscle-spindles possess a similar structure to the ordinary motor end-plate; (*b*) he has seen motor end-plates in muscle-spindles which did not contain a single sympathetic ending; (*c*) when the sympathetic chain was removed and degenerated, these small end-plates remained intact; (*d*) in an adult cat, the anterior and posterior spinal roots were cut so as to degenerate the somatic motor component and leave the sensory component intact. He figures a muscle-spindle in which the sensory ending is intact and only the degenerating remains of the motor-plate are present; and, (*e*) after section of the motor roots, the spindle muscle-fibers degenerate more slowly and not so completely as the ordinary skeletal muscle-fibers. From these observations, he is convinced that the presence of spinal motor innervation to the muscle-spindles is free from doubt. He is inclined to believe that there is a sympathetic innervation of spindle muscle-fibers but does not show any illustrations of them nor does he describe them.

After having presented nine different reasons against the Hunter and Latham (41) conception that some muscle-fibers receive only spinal innervation and others only a sympathetic one, Boeke states in conclusion ((15), p. 632) that the conception of Hunter and Latham is incorrect and not in agreement with the facts. This paper is mainly a summary of work which has been published before, with some additions. The most interesting of these, was the attempt to answer Wilson's (67) criticism of the eye-muscle experiments, by describing experiments where longer and shorter degeneration times were used.

Stefanelli (60) confirmed Gemelli (31) in his work on the nerve-endings in *Lacerta muralis* and *viridis*, and did not accept the idea of

sympathetic hypolemmal endings to skeletal muscle. Aoyagi (2) found endings similar to the accessory endings of Boeke in the intercostal muscles of a human fetus, in the tongue-muscles of talpa, in the back-muscles of lacertians, and in the pectoral muscle of *Sturnus vulgaris*. These observations were all made in normal muscle and are unconvincing.

In a series of six cats, Agduhr (1) cut the dorsal root distal to the ganglion and also the ventral root in C5, 6, 7, and 8 and T1 and 2 on one side. This was done in a manner that would not damage any sympathetic fibers from the stellate ganglion to the extremities; and at the same time the somatic nerves were removed from their cells of origin. He used five to ten days for degeneration of the somatic nerves, but his figures are taken from five- and six-day material. Agduhr recognized the presence of unmyelinated collateral motor branches which "should be equally resistant to degeneration as the sympathetic nerves can be." He stained with the Bielschowsky method. In a foot-note, he states that he carried out a set of experiments, using forty-five days' degeneration time with identical results. His conclusion was: "Thus we have in striated extremity-muscles in the cat besides hypolemmal and epilemmal cerebrospinal end-organs also hypolemmal and epilemmal sympathetic nerve-organs and thus, probably, both centrifugal and centripetal sympathetic nerves." As figured, these endings were supplied by very short unmyelinated fibers, possibly collaterals of spinal motor fibers which had resisted the short degeneration time.

In the muscle-spindles of these preparations, Agduhr observed fine non-medullated nerve-fibers belonging to muscle-fibers at the peripheral ends of the muscle-spindle and also to its capsule. These endings are unconvincing. In his Figure 11, is seen what might be a sensory ending in the spindle, and for that reason there is some doubt whether all of the somatic component is degenerated. Agduhr suggests that these endings are sympathetic sensory. Their occurrence at the peripheral ends of the spindle leads one to question whether he is not dealing with the somatic motor innervation in some cases In a series of four cats, Agduhr removed the stellate ganglion on one side and allowed one, three and six days for degeneration. In one animal after just glancing through the preparations of six days' degeneration material, he observed no sympathetic nerves or end-plates.

Terni (63) studied the distribution of the caudal sympathetic nerve

in reptiles. Sympathetic fibers were found going to skeletal muscle, but no endings were seen. In Langley's study of the nerve-fiber constitution of peripheral nerves and nerve-roots (51), cutaneous nerves were found to contain many non-myelinated fibers, while nerves to muscle contained but few. After considering the various possibilities for the distribution of the sympathetic fibers to skeletal muscle, Langley said, page 392: "So far as these facts are concerned the simplest hypothesis is that the non-myelinated fibers do not supply the muscle fibers." The work of Shimbo (59) is of little value for he endeavors to apply the Weigert method in a study of unmyelinated fibers.

Boeke's degeneration experiments were confirmed by Kuntz and Kerper (47) with both gold-chloride and the pyridine-silver method. Four weeks after section of the seventh, eighth and ninth thoracic nerves proximal to the rami communicantes in dogs, the eighth intercostal muscle was examined. Myelinated fibers were found degenerated, while the accessory fibers and endings of Boeke were still present. In another experiment, the mandibular nerve of a dog was cut intracranially and the masseter and pterygoid muscles were examined. Boeke's results were again confirmed. These fibers and endings were not illustrated.

Langworthy (53) cut the hypoglossal nerve on both sides in the white rat, and allowed two weeks' degeneration time. By this means, the component from the lingual with the chorda tympani branch of the facial was isolated. Methylene-blue preparations were made and non-medullated fibers were present in the arterial walls. "Often times fibers were noted which separated from the arterial net or dipped down from the cutaneous group to enter the musculature. There they ended in fine dust-like nerve endings upon the sarcolemma of the muscle fiber." Some of these endings terminated near motor end-plates, while others ended in long arborizations upon the fibers showing no trace of somatic endings. In this work the possibility that these might be sensory endings was not excluded. In an earlier paper the same year, Langworthy (52) says, "After the hypoglossal nerves (cat) were cut and allowed to degenerate, only a few nerve fibers of small caliber were found in the musculature apparently running with the arteries." No dust-like endings were described here.

In discussing the possibility of sympathetic accessory fibers in the

frog, Murray (54) is frank in stating (page 377): "Provisionally, then these fine fibers must be regarded as motor, and as perhaps being branches of the ordinary motor fibers, while remembering that they may possibly belong to the sympathetic supply." He described a fine unmyelinated fiber and its ending in the frog-muscle, but never goes beyond suggesting the possibility that it may be sympathetic. He found nothing that even resembled the sympathetic accessory fibers in the muscles of the pectoral fin in *Squalus acanthias*.

INNERVATION OF SKELETAL MUSCLE ACCORDING TO KULCHITSKY

In his earlier 1924 paper, Kulchitsky (43) employed the gold-chloride method in his study of the python muscle. He found unmyelinated fibers ending in *terminaisons en grappe* epilemmally in skeletal muscle. It has been noted that Boeke (15) believed they were hypolemmal in *Tropidonotus natrix*. Kulchitsky thought that these fibers were motor and thought that it "was quite possible that these non-medullated fibres are motor fibres belonging to the sympathetic system." He also described *terminaisons en grappe* supplied by non-medullated fibers in the encapsulated part of the muscle-spindle Here again he believed that it was "probable that they do not belong to the cerebrospinal nervous system but to the sympathetic." The occurrence of these *terminaisons en grappe* on smaller muscle-fibers and in the muscle-spindle led Hunter (39, 40) to believe that in skeletal muscle there are two innervations, somatic motor to larger muscle-fibers and sympathetic motor to smaller ones. Boeke (15) criticised this conception in a most convincing way.

Later in this same year, Kulchitsky (44) used the methylene-blue method in studying the nerve-terminations in the frog. He described, in addition to the medullated fibers of the cerebrospinal system, non-medullated ones. These were sensory and terminated epilemmally in leaf-like expansions, resembling the endings described by Huber (37) in the extrinsic eye-muscles of the rabbit. Kulchitsky did not see the sympathetic accessory endings, and his position toward specialized sympathetic endings is far more doubtful than in his paper earlier in the year. It is interesting to see the change in attitude toward epilemmal endings; in the python they were considered as motor and in the frog, as sensory. In the latter, however, they were seen to occur on the same fiber with the motor end-plate.

Hunter and Latham (41) applied the gold-chloride method to the

limb, intercostal, extrinsic and sometimes the intrinsic eye-muscles of fowls, sea gulls and goats. They satisfied themselves that there was "little evidence incompatible with the theory that these striped muscles are divided into alternate groups of muscle-fibers served respectively by branches from the somatic and sympathetic nervous systems, the former subserving contractile, the latter plastic tonus."

After the somatic denervation of the wings of birds, Hunter (40) found many normal muscle-fibers in groups among the diminutive degenerating fibers. The conclusion was made that the fibers which resisted degeneration were the ones which subserved plastic tonus and received only a sympathetic innervation (were still intact). In goats when only the lumbar sympathetic chain was removed and degeneration time allowed, a large number of small fibers were found in cross-sections. These diminutive fibers were accounted for as degenerating fibers which subserved plastic tonus and degenerated after removal from their nerve-supply which was said to come only from the sympathetic nervous system. Hunter diagrams in this paper a dual innervation of skeletal muscle. The arc for contractile tonus was subserved on the afferent side by endings in the muscle-spindles and on the efferent side by the ordinary myelinated motor fibers, terminating in motor end-plates. The arc for plastic tonus was subserved on its afferent side by epilemmal endings on the thin muscle-fibers coming from non-myelinated fibers; on its efferent side by non-myelinated fibers ending hypolemmally in grape-like terminations in the thin muscle-fibers and in the intrafusal muscle-fibers of the muscle-spindles.

Bielschowsky (3) according to Cobb (22) found that the end-organs described by Boeke are most numerous in the external ocular muscles, less numerous in the facial muscles, and very occasional in the muscles of the extremities. He believes these are sympathetic nerve-endings because they are non-myelinated throughout their whole course. However, this is poor proof in view of the fact that it is exceedingly difficult to determine the origin of non-myelinated fibers in the muscle in the absence of experimental procedures. Garven (30) described four types of accessory fibers in the panniculus carnosus of the hedgehog, but inasmuch as these observations were made on normal material, it is impossible to say that these endings give proof of the dual innervation of skeletal muscle. In his gold-chloride preparations Garven was unable to trace endings of accessory fibers in muscle-spindles of the hedgehog, in the striated muscle of frog, in the

lizard, extrinsic eye-muscles of the rabbit, and in human pectoral muscle. Unmyelinated fibers could be found in each case, but it was impossible to trace the endings which might as well have been on blood-vessels as on muscle-fibers. Kuré and his co-workers (48) used the Bielschowsky and Cajal methods on a series of ten cats, young and old. In these observations, made on normal muscle, it is interesting that they found what they called sympathetic accessory end-plates in the eye- and tongue-muscles and in the triceps brachii. In other muscles they saw unmyelinated fibers of autonomic nature between the muscle-fibers, but they could not find Boeke's sympathetic accessory endings. They attributed their negative results to difficulties in staining. After removal of the thoracicolumbar sympathetic supply to the ear-muscles in the rabbit and allowing from two weeks' to three months' degeneration time, Feldburg (28) was unable to observe any degeneration or decrease in the muscle-fiber size such as Hunter described for the goat.

Tello (62) could not find sympathetic accessory fibers ending in skeletal muscle. The author has not seen the paper of Del Rio Hortega (Boeke (14), p. 102) nor that of Cajal (21). According to Boeke (14), both of them doubt the existence of sympathetic accessory fibers. Cajal, like Tello, has not been able to demonstrate the existence of accessory sympathetic fibers (adult cat and rabbit). He thinks that the histological demonstration of such fibers is difficult. He found it nearly impossible to distinguish with certainty a fine unmyelinated collateral of a myelinated motor fiber at some distance from its origin, from a purely sympathetic fiber. It is evident that the workers in the Madrid laboratory are very skeptical as to the sympathetic innervation of skeletal muscle.

Iwanaga (42) examined the tongue, laryngeal, intercostal and extremity muscles of man with a modified silver method. Only twice (in the muscle of the vocal cord) in all these preparations did he see anything like Boeke's accessory fibers. In the posterior cricoarytenoid, thyreohyoid, and other small muscles he was unable to find a single accessory fiber. In the eye, he saw only a very few of these endings.

Woollard (68) observed a variety of normal mammals; mammals suffering from deficiency diseases; cats in which the abdominal sympathetic had been removed on one side; cats in which the ventral roots of the lumbosacral plexus had been divided. He used the

gold-chloride method, staining with silver as modified by Boeke, and the intravitam methylene-blue method. The latter gave the clearest pictures and, furthermore, the fibers could be followed for great distances in flat preparations. The results were entirely negative in regard to the double innervation, either of the Kulchitsky type or of the Boeke type, except in the case of the ocular muscles. Due to the fact that the ocular muscles resembled those of the tongue and the diaphragm, special attention was given to the latter, with negative results. In the external ocular muscles, Woollard distinguished a thick and a thin type of muscle-fiber, the latter being associated with non-myelinated fibers. Although these observations were made on normal ocular muscles, he regards these non-myelinated fibers as sympathetic fibers which behave not according to the Boeke idea but according to the Kulchitsky description. However, degeneration procedures, carried out in a more convincing manner than any yet reported, would have to be made in order to establish the sympathetic origin of these fibers. According to Woollard (69, 70), Da Castro, as the result of his experimental investigations, has been unable to confirm the findings of Boeke.

Kuntz (45) used three to six weeks' degeneration time for the somatic innervation in dogs. With pyridine-silver technique, he again confirmed Boeke. He believed that he had ruled out the possibility of regeneration.

Hinsey (35) isolated the sympathetic component to the small muscles of the hind-limbs of adult cats. When regeneration was prevented, he could see the postganglionic sympathetic fibers in the vascular plexuses but he did not see these fibers leave the plexuses to end hypolemmally in skeletal muscle stained with the pyridine-silver method.

According to Weed (65), Hines has traced non-myelinated fibers into the typical motor end-plates of myelinated nerves in methylene-blue preparations of frog-muscle. By degeneration experiments, these were shown to be sympathetic. Hines and Tower (34) failed to find that the sympathetic nervous system takes any part in the innervation of the intrafusal fiber itself in the kitten. While unwilling to commit themselves in regard to a participation of the sympathetic nervous system in the innervation of the ordinary muscle-fiber they make a suggestive statement in one of their protocols. The C7 C8, and T1 dorsal root ganglia and the corresponding ventral roots were

resected in a four-months' old kitten. Four days later, the animal was killed and injected with methylene-blue. These investigators say ((34), p. 281), "The interossei muscles on the right side were studied in detail. Nerve-fibers were found intact running along blood-vessels and these were the only ones which were normal. All other nerves were in a process of degeneration. All motor nerves to the skeletal muscle-fibers (Fig. 6 *a*) and all nerves (Fig. 6 *b* and 6 *c*) passing to the intrafusal fibers of the muscle-spindle were in a process of degeneration."

Attention should be called to a number of the factors which may give rise to misinterpretation of morphological findings in skeletal muscle. Cajal (21) objected to the use of embryonic and young muscle in a problem of this kind. He raised the question whether the accessory fibers and other structures described by some authors in the fetus and in young animals might not be considered as anomalous structures destined, at least in part, to disappear in the adult or to be transformed considerably. Here in case the development were incomplete, there might be unmyelinated fibers, later becoming myelinated, simple endings which would become more complex, and some fibers which although present in development might have disappeared in the adult. Furthermore, the finding here and there in adult muscle of these embryonic structures would be possible, it would seem, and need not be considered in the adult muscle as being of sympathetic origin. In some muscles, eye- and tongue-muscles especially, the presence of unmyelinated collateral motor fibers must always be considered. Just because it is not possible to trace one to a myelinated fiber, is not conclusive evidence that it is not derived from a myelinated motor fiber at some point farther back.

Inasmuch as there is a difference in the appearance between embryonic or young and adult muscle, a difference might be found to exist between the muscles of amphibians, reptiles, birds and mammals. The mere fact that one is able to show an unmyelinated fiber which can be followed for some distance without branching from a myelinated fiber in the frog or in the python, does not permit the conclusion that it is a sympathetic fiber. In the lower vertebrates the only evidence which would be conclusive would be that from degeneration experiments. Here again it would be necessary to be sure that sufficient time had been allowed for degeneration time—a much longer period than that required in warm-blooded animals.

A great many of the degeneration times which have been used have been far too short. In the consideration of selecting a degeneration time, one should have in mind, not the degeneration of the myelinated fibers and their endings; but, instead, of the unmyelinated fibers and their endings. Ranson (56) found that a few non-medullated fibers may persist for two or three weeks in the peripheral stump of a sectioned nerve. Agduhr realized that unmyelinated collaterals of motor or sensory fibers might be just as resistant to degeneration as sympathetic fibers. Boeke and Dusser de Barenne (16) state that it is possible to find here and there in sections seemingly intact, non-medullated nerve-fibers as long as fourteen days after the dissection of the nerve. If the nerve-fibers were intact, it may be questioned whether the endings might not also have been present. The persistence of unmyelinated fibers over short degeneration times may have been a confusion point in a number of the experiments, especially where silver stains were employed.

Huber, Crevatin and Dogiel have shown the presence of unmyelinated fibers with grape-like endings, most of which at least, are ultimately branches of myelinated fibers. These are said to have a sensory function. Boeke found similar endings in the tongue of the hedgehog. Possibly other muscles in which muscle-spindles are lacking or are poorly developed, have similar terminations, which are probably proprioceptive in function. These unmyelinated fibers degenerate more slowly than myelinated ones. The persistence of some of them may account for some of the accessory fibers and endings reported in the eye- and tongue-muscles of mammals. In addition, endings of this type may have been taken for sympathetic fibers in lower vertebrates. Of course, it may be argued that the size and epilemmal position make it easy to distinguish these endings, but that this is an unreliable method; and, furthermore, if reliable, that it has been disregarded in some of the interpretations. It might be well to recall at this time the difficulty Kulchitsky had in determining the position of his *terminaisons en grappe*. He believed these to be epilemmal and sympathetic, and Boeke thought most of them hypolemmal and cerebrospinal motor. Differential size of unmyelinated fibers has been of little value in settling this question. The trouble has been that any unmyelinated fiber with a grape-like termination which will withstand three to five days' degeneration has been considered sympathetic, and the author feels that this has led to many misinterpretations.

When the somatic innervation is completely degenerated, there remains the vascular plexus, which contains sympathetic fibers. As Langley (50) pointed out, "The essential point is whether fibers from this plexus form nerve-endings under the sarcolemma of the muscle-fibers or whether they all end in connection with blood-vessels." The muscles are very well supplied with blood-vessels and caution should always be exerted to be sure that endings do not belong to the vessels rather than to the muscle-fibers.

When longer degeneration periods are utilized for the somatic component, the possibility of regeneration is present. The difficulty which would be experienced in recognizing these regenerating fibers is expressed in Boeke's own words, ((10), p. 85): "Kurz es wird in den allermeisten Fällen unmöglich sein, die regenerierten accessorischen Fasern von diesen Fasern (thin unmyelinated sensory fibers, ultra-terminal fibers, and unmyelinated motor-fibers) zu unterschieden." In the early stages of regeneration, it would be extremely difficult to avoid confusion, due to the fact that there are regenerating structures which could not be differentiated from the accessory fibers and endings which Boeke described. The possibility of regeneration was not given sufficient consideration in the interpretation of the work of Boeke and Dusser de Barenne (16) and other experiments of a similar nature.

The objection may be raised that the staining technique used in negative results has been unsuitable to stain the sympathetic accessory fibers. Cajal and Tello, using the Cajal silver method, have been unable to demonstrate them. Woollard has been unsuccessful with the gold-chloride, Bielschowsky and methylene-blue methods in all the muscles of the mammals he used, with the possible exception of the external ocular muscles. Hinsey has been unable to demonstrate them with the pyridine-silver method in the small muscles of the hind-foot of the cat. It would seem that if they are present, some of these observers would have seen them.[2]

[2] Dr. H. J. Wilkinson of the Department of Anatomy of the University of Sydney, Australia, has recently published the results of his investigations on muscle-innervation (66). In examining the innervation of the muscles in different representatives of the vertebrate system, he used the gold-chloride, methylene-blue and silver techniques. In his extensive research, he has been unable to find any evidence of the sympathetic innervation of skeletal muscle. It was his privilege to examine the preparations of Boeke and Agduhr, but he has formed a different opinion regarding the identity of the endings seen. In his article, he asserts that all these endings are somatic and not "sympathetic," and he gives the reasons for his opinion.

INNERVATION OF SKELETAL MUSCLE, ACCORDING TO HINSEY

Figure 35 is a diagram which represents the author's conception of the innervation of the skeletal muscles in mammals. The somatic afferent component is made up of fibers whose cells of origin are in the posterior root ganglia. Here are found fibers of all the different sizes.

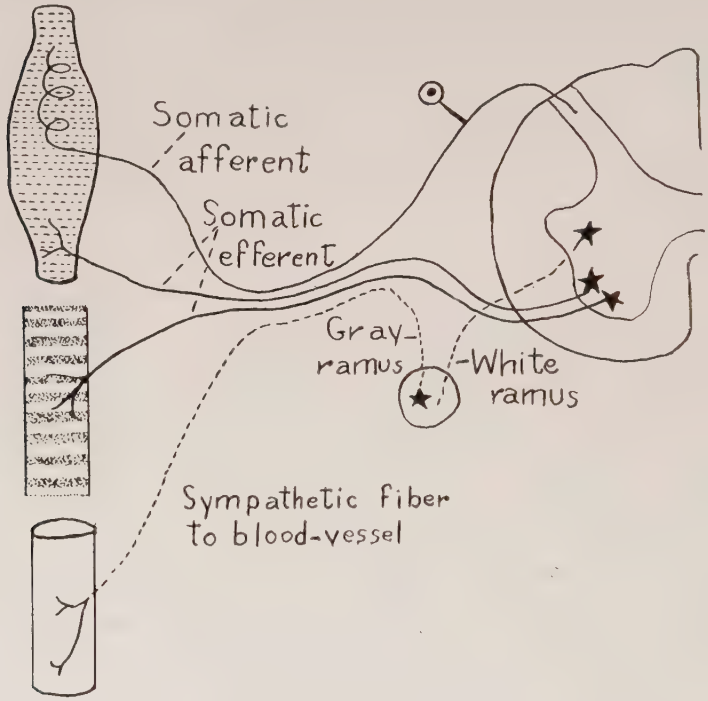

Fig. 35. A diagram illustrating the author's conception of the innervation of skeletal muscle in the cat; showing the innervation of a muscle-spindle, an ordinary skeletal muscle-fiber, and a blood-vessel. The sensory innervation to the blood-vessel is not shown in this diagram.

The larger myelinated fibers pass to endings in muscle-spindles, tendon-spindles, Pacinian corpuscles and any other types of encapsulated endings which may be present. The smaller myelinated and unmyelinated pass to endings free in the connective tissue of the adventitia of blood-vessels, perimysium and endomysium, sometimes close to muscle-fibers. The somatic efferent component is made of

myelinated fibers whose cells of origin are in the anterior horn. These fibers pass to motor terminations in the ordinary skeletal muscle-fibers and in the intrafusal fibers of muscle-spindles. Cells in the intermediolateral cell-column give rise to the small myelinated preganglionic sympathetic fibers which pass over the ventral roots, out through the white rami to the chain-ganglia of the sympathetic trunk. Here the pre-postganglionic synapse occurs. The post-ganglionic neurones in the ganglia give rise to the postganglionic fibers which may be myelinated or unmyelinated. They pass out over the gray rami to the spinal nerve and reach the vessels of the muscles

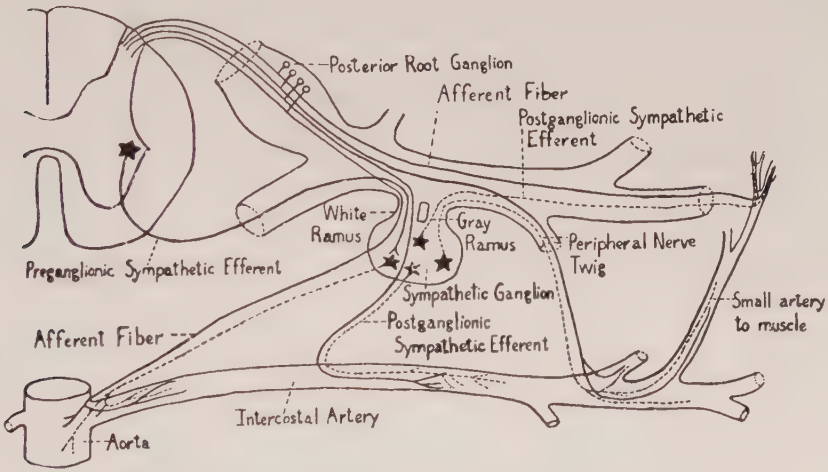

Fig. 36. Diagram of the innervation of blood-vessels. The afferent fibers with cells of origin in the posterior root ganglion are shown in solid lines. Postganglionic sympathetic efferents with cells of origin in the sympathetic chain-ganglion are shown in dotted lines.

by way of twigs or branches of the peripheral nerves to form the vascular plexus. The author has never seen these fibers leave the vascular plexus to end hypolemmally in skeletal muscle-fibers.

INNERVATION OF BLOOD-VESSELS

The literature pertaining to the innervation of the blood-vessels has recently been reviewed by Stöhr (61) and by Hinsey (36). This discussion is, therefore, concerned mainly with the innervation of the blood-vessels of skeletal muscle as seen in the cat. Figure 36 is a

diagram of the probable innervation. A thoracic level has been taken so as to show the pre- and postganglionic relationships. The vessels in the splanchnic area receive visceral branches from the sympathetic trunk which contain both sensory and sympathetic motor fibers. These form a plexus about the vessels in this area which may send fibers some little distance peripherally. According to Woollard (68), in the cat, fibers from the aortic plexus may extend as far down as the bifurcation of the femoral artery. The vessels in the somatic area are supplied by branches from the peripheral nerve.

The sensory component is shown in solid lines in the diagram. The cells of origin are in the posterior root ganglia. These fibers pass to the vessels in the splanchnic region mainly by way of the white rami, although Langley's work (49) indicates that a very few may pass over the gray rami. These fibers pass to the vessels by way of the visceral branches of the sympathetic trunk. The work of Langley (49) and that of Kuntz and Farnsworth (46) shows that a few of these fibers may pass back by way of the gray rami to the spinal nerve. The vessels of the somatic area receive their sensory supply from branches of the peripheral nerves. These sensory fibers in the muscle are small myelinated and unmyelinated. They terminate in the adventitia of the vessels and may be traced as far as the terminal arterioles.

The preganglionic sympathetic efferent fibers are small myelinated and their cells of origin are in the intermediolateral cell-column. These pass to the sympathetic trunk by way of the ventral root and the white rami. The postganglionic neurones in the chain-ganglia send some of their fibers out over visceral branches to reach the blood-vessels of the splanchnic area; while they send others back by way of the gray rami to the spinal nerves and from there by way of peripheral branches to vessels in the somatic area. These postganglionic sympathetic fibers supply all vessels with smooth muscle and a very small part of the capillary bed in skeletal muscle. In the muscle no ganglion-cells are seen in relation to the vessel walls. All of the postganglionic neurones giving origin to the vasoconstrictor fibers to muscles of the extremities of the cat are found in the sympathetic chain-ganglia, so that removal of the lumbar sympathetic trunk should completely denervate the vessels of the extremities. From the anatomical point of view, gangliectomy rather than periarterial sympathectomy should be the rational procedure in cases of Raynaud's and other vascular diseases which are benefited by the removal of the vasoconstrictor impulses.

DISCUSSION

The following questions submitted to Dr. Hinsey, together with the answers to them, are here reported verbatim.

Dr. Ranson: Dr. Hinsey's work has been done, as he has told you, with a silver stain, which necessitated the cutting of relatively thin sections. Therefore, it forms a counterpart of the work which Dr. Hines has done using whole mounts with methylene-blue stains. They are in agreement on one very fundamental point; that the fibers in the muscle-spindles of the cat receive no sympathetic fibers.

I should like to ask Dr. Hinsey a question in regard to the work of Boeke on the eye-muscle. These unmyelinated fibers which he saw, ending in such great numbers in the eye-muscles, resembling somewhat the fibers which Dr. Huber described many years ago in the eye-muscles and which Dr. Huber believed were sensory—I wonder what Dr. Hinsey thinks of the possibility that those two fibers might be the same, Boeke's fibers and Dr. Huber's fibers?

Dr. Hinsey: In regard to the eye-muscle studies of Boeke, the first part was rather unsatisfactory, because a parasympathetic innervation that was derived from the path of the cranial nerves to the eye-muscles was described in addition to a thoracicolumbar sympathetic component.

In the early work, when the nerves to the eye-muscles were cut and allowed to degenerate three weeks, the connections of these unmyelinated fibers with the skeletal muscle-fibers in the eye-muscles were not so clear as in other preparations with shorter degeneration times, and Boeke has not figured them. These unmyelinated fibers were probably associated with the vascular innervation. In his 1927 work (15), he says that he has given longer degeneration times and that he thinks now that more of these endings in the eye-muscles are of thoracicolumbar sympathetic origin.

I wish to say that the findings on the muscles of the limb cannot be applied to the muscles of the eye particularly. This point has been brought out by Dr. Hines, but we feel that those small myelinated and unmyelinated fibers of sensory nature, which Huber described years ago and which have also been described by Crevatin and Dogiel, serve as a confusion point and, unless we can be sure that these endings are hypolemmal, we still have the possibility that they may be sensory.

In the work of Woollard, he did not carry out degeneration experiments on the muscles of the eye. He used methylene-blue preparations and was unable to find these sympathetic endings on the muscles of the extremities, of the trunk, and of the tongue and diaphragm, but he did find a veritable forest of unmyelinated fibers in the eye-muscles. Although he did not approach the problem experimentally in the muscles of the eye, he was inclined to think there was a possibility that some of these unmyelinated fibers in the eye muscles were sympathetic in origin. They were not seen to end on the same muscle-fibers on which the myelinated fibers terminated. The muscle-fibers upon which these smaller unmyelinated fibers terminated were of the small variety.

I am not so sure that the experimental work upon the muscles of the eye is conclusive because the degeneration time in a great many instances has been only

three and one-half and five days. Longer degeneration times with exact accounts of experimental details have not been reported.

Dr. Ferraro: Am I correct in my understanding that there are no unmyelinated fibers in the ventral root?

According to the data which are found in Greving's monograph on the sympathetic nervous systems, unmyelinated fibers follow the anterior roots and reach the sympathetic or lateral chain. It seems to me, therefore, that this question is not settled, as it might appear to be from the statement of Dr. Hinsey.

There is another question I should like to ask Dr. Hinsey,—if he can tell me how the sympathetic fibers reach the lateral chain after the section of the ventral and dorsal roots. Does he think that fibers originating in the upper or lower segments of the sympathetic system may reach the level in question, or does he think that recurrent fibers of the parasympathetic system may reach the lateral chain and then the peripheral muscular apparatus?

Dr. Hinsey: In regard to the presence of unmyelinated fibers in the ventral roots, all I can say is this: When we remove the thoracicolumbar sympathetic chain from the second lumbar sympathetic ganglion to below the brim of the pelvis and then remove the dorsal root ganglia of the fourth, fifth, sixth, seventh lumbar and the first sacral nerves, we find, in pyridine-silver preparations, no unmyelinated fibers in the muscle-branches of the femoral nerve. That is all that I can say in regard to the matter.

In regard to the arrangement of the parasympathetic fibers, my work has not been experimental along that line so that I cannot speak from experience. We do know however that the preganglionic outflow in the cat reaches the lateral chain through the white rami and that the preganglionic outflow for the lumbosacral plexus in the cat comes from the lower thoracic and upper lumbar segments as low as the second or third lumbar segment. When we section the dorsal and ventral roots of L4, L5, L6, L7 and S1, the preganglionic fibers to the chain have not been sectioned, inasmuch as they reach the chain through white rami at a higher level.

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Section III

PHYSIOLOGY

CHAPTER IX

THE SYMPATHETIC DIVISION OF THE AUTONOMIC SYSTEM IN RELATION TO HOMEOSTASIS[1]

WALTER B. CANNON, M.D.

INTRODUCTION

THE living parts of complex organisms, such as human beings, do not come into direct contact with the surrounding air. They are separated from the air by a layer of mucus or by a layer of dead, horny skin. The actually living parts are embedded in the fluids which bathe the cells—the blood or the lymph. These fluids, as Claude Bernard (5) pointed out a half-century ago, constitute the *milieu interne* or internal environment. This internal environment, or as we may call it, the *fluid-matrix*, of the living structures, is a product of the organism itself, developing as the organism develops. Furthermore it is controlled by the organism. As in the course of evolution organisms have become more perfect it is noteworthy that they have become gradually more free from changes in the external environment; more free, for example, from changes of humidity, changes of temperature, and variations of oxygen tension. This achievement of freedom from disturbance in spite of extensive changes in the outer world, has been brought about by mechanisms which maintain uniformity of the fluid-matrix. Claude Bernard clearly recognized this fact when he stated that "it is the fixity of the *milieu interieur* which is the condition of free and independent life." He further declared that "all the vital mechanisms, however varied they may be, have only one object—that of preserving constant the conditions of life in the internal environment."

One might speak of the steady states which are maintained in the fluid-matrix of the body as equilibria. Thus there would be the equilibrium of temperature, the equilibrium of sugar in the blood, and of the oxygen tension in the tissues. The term *equilibrium*, however, as used by physicists, chemists and physical-chemists, has come to

[1] From the Laboratories of Physiology, Harvard Medical School.

have a fairly exact meaning in relation to physicochemical processes. There are, of course, such processes in the body but many of the steady states, as illustrated by the cases just cited, are dependent upon "reactions" which are peculiar to the organization of living beings. These reactions are much more complex and indirect than the ordinary physical and chemical adjustments, i. e., they are peculiarly physiological. Under these circumstances it has seemed to the author that a special designation is desirable. Accordingly he has suggested (10) that the general idea of uniformity or stability in the organism be called *homeostasis*, a term the meaning of which is clear and the other forms of which, as in the adjective *homeostatic* and in the generic term *homeostatics*, are likewise clear and descriptive.

The great importance of homeostasis is well illustrated by noting what occurs when the mechanisms maintaining it are lacking. The frog, so commonly used in the physiological laboratory, has no temperature regulating mechanism. The only way in which the animal can survive the cold northern winter is by sinking to the bottom of a pool when cold weather comes and living in the mud during the winter months. The animal likewise has no means of maintaining its water-content, and if left in the dry air of the laboratory for a day or two, it becomes as desiccated as a mummy. Higher forms, such as the birds and mammals, have developed mechanisms for protection against such dangers. They have arrangements for maintaining a fairly constant temperature and for preserving the water-content of the body, and devices also for stabilizing other highly important conditions for the cellular functions.

The rôle which the vegetative nervous system plays in the mechanisms of homeostasis can best be approached by calling attention to the different parts which the voluntary and the involuntary nervous systems play. The voluntary nervous system, or, to use physiological terms, the cerebrospinal nervous system, is connected with receptors on the body surface and with effectors in the skeletal muscles which operate the bony lever systems of the body. It is through this system that man becomes acquainted with the vast ranges of his environment, from the object which touches him, to the remotest star, incredible light-years distant from him; and it is through this system that he causes all of the extraordinary changes in his surroundings, from building skyscrapers, airplanes, and ocean liners to turning on the radio. This system, by means of which one learns of his sur-

roundings and acts and reacts upon them, may be considered as the *exterofective system.* Every response of this system, even the slightest, is associated with the using up of oxygen and energy-yielding material and at the same time with the production of waste. Consequently the activities of the exterofective system are continuously producing changes in the fluid-matrix of the body. In order that the internal environment shall be maintained in a uniform state, external activity must necessarily be mirrored in an internal adjustment. The author wishes to introduce evidence that the system which manages these internal adjustments is in the main the sympathetic division of the autonomic system. This system which innervates smooth muscle (and, incidentally, cardiac muscle) and glands, may be regarded as an *interofective system*, managing the *internal* affairs of the body. And of the autonomic system the sympathetic division is especially concerned with keeping the organs fit for action. It mobilizes the bodily forces and is a stabilizing agency when homeostasis is threatened. The functioning of the sympathetic division as an agency of homeostasis can be made clear by illustrations.

The changes may now be considered which are brought about by vigorous muscular effort,—the sort of activity of the exterofective system that is evoked by strong and repeated stimulation.

THE EFFECTS OF MUSCULAR ACTIVITY

1. Sugar Consumption

The activity of muscles is associated with the using up of sugar. Indeed, continuous muscular activity will considerably reduce the sugar in the blood. It has recently been shown (8) that after two hours in a treadmill the average level of blood-sugar in dogs falls from about 90 mg. per cent (i.e., per 100 cc. of blood) to about 66 mg. per cent. That this fall occurs in spite of a constant renewal from the liver is proved by the fact that continuous prolonged exercise will deplete the liver of its store of glycogen (19). If the liver is extirpated the ordinary functioning of the body soon reduces the blood-sugar to a point at which convulsions and coma lead to death (20). An overdose of insulin brings about similar dire results unless the blood-sugar is increased in amount (2). It is obvious, therefore, that the lowering of the glycemic level may cause serious danger. The mechanism whereby danger is avoided is operated by the sympathico-

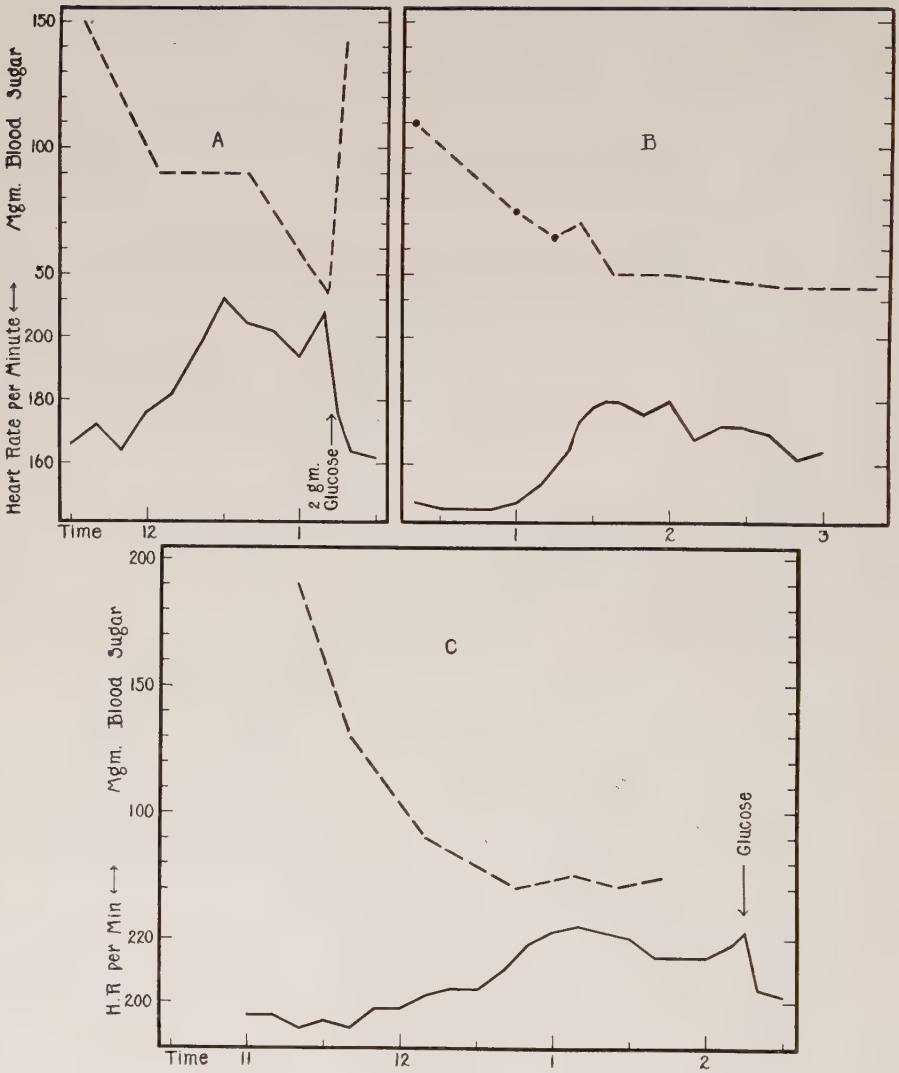

FIG. 37. Increase in rate of the denervated heart (solid line), in animals under chloralose anesthesia, when the falling blood-sugar concentration (dash-line) passed a critical point. In Case *A*, the insulin was injected into the jugular vein at 11:33; in *B*, at 11:08; and in *C*, at 9:30. In each case, 4 units per kilo of body-weight were injected.

adrenal apparatus. As was shown by McIver, Bliss and the author (12) some years ago, a reduction of the blood-sugar to a point between 70 and 80 mg. per cent is associated with the stimulation of the sympathico-adrenal mechanism. They used the denervated heart, which is extremely sensitive to an increase of adrenin in the circulating blood, to indicate (by a faster beat) an increased adrenal secretion (Fig. 37). The lower the sugar-level falls below 70 mg. per cent the greater the activity of the sympathico-adrenal apparatus, and if the sugar percentage falls to the convulsive level the activity of the apparatus is maximal. The action of this apparatus liberates sugar from storage in the liver and consequently the rapid drop of the glycemic percentage is checked (Fig. 37). If the agency (insulin, in the author's experiments) which is lowering the blood-sugar is not overwhelmingly affective, the sympathico-adrenal apparatus liberates so much sugar from the liver that the danger is passed and the apparatus which has been called into activity subsides into inactivity. By the artificial introduction of glucose into the blood-stream the protective service rendered by the sympathetic system and the adrenal medulla may be dropped quickly from a high degree of vigor to complete quiescence (Fig. 37). As was shown in 1927 (13), mere motion, such as walking a short distance across the floor, is accompanied by the bringing of the sympathico-adrenal mechanism into service. It is clear that even slight activities of the exterofective system are accompanied by corresponding activities of the interofective system. Because of these associated activities the sugar-level is maintained above the dangerous region in spite of great demands for sugar from laboring muscles.

2. Heat-Production

Vigorous muscular activity is associated with the development of heat. Indeed, under usual circumstances about 75 per cent of the energy of muscle appears in the form of heat. If large muscle-masses, like those found in both legs and in both arms, are brought into supreme action in rapid repetition, as they are in a four-mile rowing race, the amount of heat produced may be enormous. Unless the heat is dissipated, the temperature of the internal environment may rise to a serious degree. At rest a man of about 150 pounds weight uses approximately 250 cc. of oxygen per minute—enough to provide about 1.25 calories, or enough, if he should lose no heat, to raise his

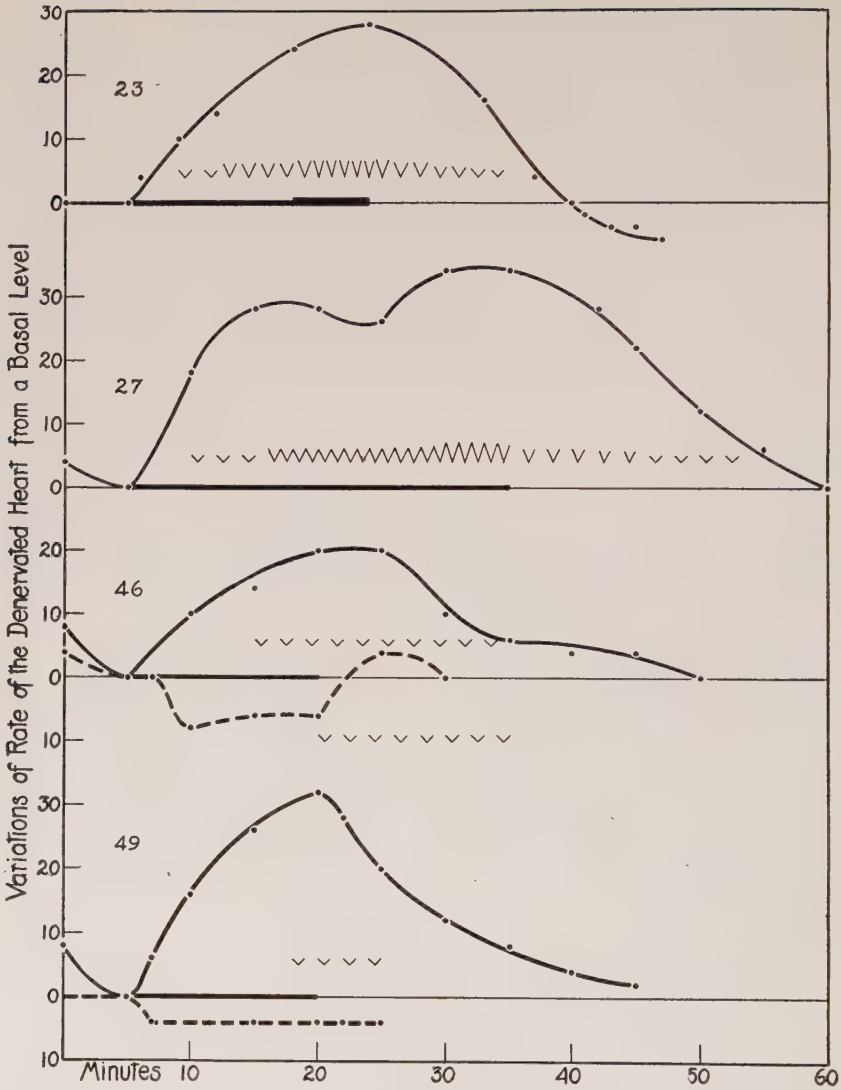

FIG. 38. Increases in rate of the denervated heart above a basal level when animals with adrenals intact (Nos. 23, 27, 46 and 49) were exposed to cold air. The period of exposure is denoted by a thickening of the base line; the double thickening in the case of No. 23 marks the time of a cold draught through an open door. Shivering is indicated by separate *v's* when it was intermittent, and by connected *v's* when it was continuous. The size of the *v's* marks roughly the intensity. The dash-lines in Cases 46 and 49 show the changes in heart-rate under similar conditions of exposure after the exclusion of the medulli-adrenal secretion.

body-temperature about 1°C. in fifty minutes. The rate of oxygen intake during steady vigorous exercise may rise from 0.25 liter to 4.5 liters—an eighteen-fold increase. This would be enough to raise the body-temperature, should there be no heat-loss, as much as 6°C. (to 109°F.)—a dangerous rise—in about eight minutes. As a matter of direct observation, temperatures of 104° to 105°F. have been reported as consequent on exertion (17). It is known that nerve-cells of the brain will not endure temperatures higher than approximately 108°F. for several hours without undergoing irreversible chemical changes (16). A high temperature of the fluid-matrix of the body is therefore, a matter of serious concern. When the blood-temperature tends to rise the sympathetic system is brought into action in two ways: there is a relaxation of the peripheral blood-vessels, the tone of which is governed by the sympathetic system, and a pouring out of sweat. The relaxation of the peripheral vessels allows a flushing of the skin with the hot blood, which may lose its heat to the exterior by convection and conduction if outer objects are cooler than the blood. The sweat which is liberated on the body-surface, evaporates if the air is not too humid and by evaporation the extra heat which is being produced is carried away. Thus the tendency towards a rise in temperature is prevented by the interofective action of the sympathetic system.

In this connection it is pertinent to mention the rôle of the sympathetic system when there is an opposite tendency, i.e., when a cold environment rapidly removes heat from the body and there is a tendency towards a fall in temperature. Under these circumstances that system again is brought into action. The hairs and the feathers are erected on animals provided with these means of keeping the body warm. Thereby more of a poorly-conducting medium, air, is enmeshed in the layers immediately around the body. Simultaneously there is a constriction of the surface vessels, which lessens the dissipation of heat through the skin. And attendant on that, or perhaps slightly later, there is, as has been shown (14), a liberation of adrenin into the blood-stream (Fig. 38). Adrenin has the effect of accelerating the processes of combustion in the body so that there is a greater production of heat at this time when more heat is required to keep the temperature of the internal environment from falling. If, in spite of the processes which lead to the conservation of heat and to the chemical production of extra heat, just mentioned, there is, never-

theless, a fall in temperature, another mechanism is brought into action (i.e., shivering), which results in a very great increase in the output of heat because of muscular contraction. Recent laboratory evidence obtained by the author, indicates that shivering is managed automatically in the region of the diencephalon where the sympathetic system has its central representation. There is no evidence, however, that shivering is induced by sympathetic impulses.

From the foregoing data it is evident that the homeostasis of the temperature of the internal environment is largely under the control of organs and agencies which are dominated by the sympathetic division of the autonomic system.

3. Circulation and Respiration

When one engages in strenuous muscular work there is a tendency for the reaction of the blood to shift towards the acid side of neutrality. This is due to the increase of carbonic and of lactic acid which are produced in consequence of the neuromuscular action. Again the change is not without danger. As is well known, in pathological states a condition of acidosis may develop to such a degree that the functions of the nervous system are impaired and, if not rectified, coma and death supervene. Long before any such stage as this is reached, as a consequence of muscular effort, respiratory movements greatly increase the ventilation of the lungs so that the excess carbon-dioxide liberated from the blood is carried away to the outer atmosphere. The muscles of respiration are in the main striated muscles and are not under the control of the sympathetic system. There are other muscles, however,—those which surround the bronchioles—which are of the smooth variety and which are subject to sympathetic control. It is known that when the sympathetic nerve-supply to the bronchioles is stimulated or when its action is mimicked by means of adrenalin, the smooth muscles relax and the lumen of the bronchioles is thereby enlarged (18). Thus the tubular passageways are accommodated to the larger ventilation in vigorous effort and the air moves to and fro with less friction. As mentioned above, there is clear evidence that the sympathetic system is brought into action even when there is minor activity of the exterofective system. It seems highly probable, therefore, that whenever one engages in strenuous exertion there is a dilatation of the bronchioles, i.e., an exhibition of the functioning of the interofective system at a time

when homesotasis of the acid-base relationship in the blood becomes important.

4. Oxygen Supply

At the same time that there is a greater development of carbonic acid as a consequence of muscular work there is a greatly increased need of oxygen. Indeed, the demand for oxygen may be greater than can be supplied although the blood-flow through the contracting muscles may be increased as much as nine times and the oxygen consumption may be increased as much as eighteen times what it is during rest (1). Under such circumstances the organism goes into an "oxygen debt" which must be paid later at a quiet time by the burning of accumulated waste.

The problem of providing an adequate oxygen supply for the tissues is met by a wider variety of devices than are invoked in meeting any other bodily need. The agencies of primary concern are the oxygen carriers, i.e., the red blood-corpuscles. Under normal conditions they leave the lungs almost completely loaded; it is impossible therefore to increase the oxygen supply by increasing the individual load. The simplest mode of increasing the supply is by increasing in a given time the number of trips made by the corpuscles from the lungs to the needy organs. This end is achieved by driving the blood largely away from the splanchnic area (by splanchnic vasoconstriction) and by accelerating the heart-beat. These two changes bring about an increase of arterial pressure which during continued muscular effort may be 50 or more mm. of mercury above the resting level (6). In consequence of this higher head of pressure the blood, flows faster, especially through such organs as the brain and spinal cord and the heart and the laboring muscles, in which the blood-vessels either do not contract in the presence of a high general arterial pressure or are actually dilated. Because of these adjustments the total circulation rate may be augmented by as much as five times and the rate through the contracting muscles, where vessels are dilated, may be, as has been noted, much faster still. In addition to this faster rate there is a greater unloading of the oxygen in the active parts. For both reasons, therefore, a greatly augmented supply of oxygen is provided.

The organism not only can make more effective use of the available corpuscles by speeding up the circulation, it can also increase the

number of available corpuscles in circulation. Recent evidence has shown that the spleen in the resting state of an animal may be three or more times as large as it is during activity or after death (4). The pulp of the resting spleen contains corpuscles in a concentrated state—from 50 to 100 per cent more concentrated than in the circulating blood (21). When there is need for oxygen, as in high altitudes,

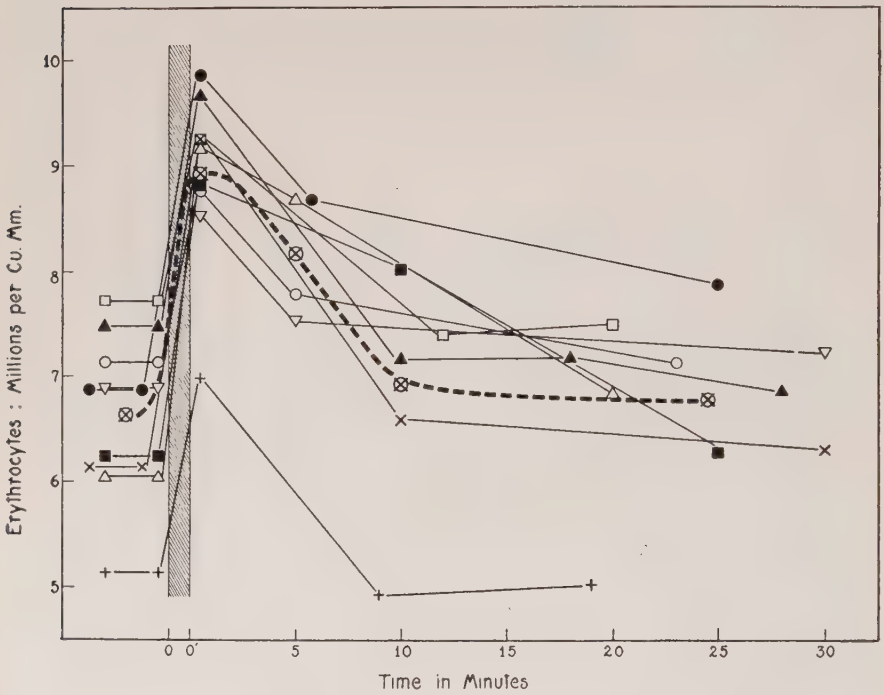

FIG. 39. The course of emotional polycythemia,—a graphic record of nine cases. The vertical, shaded band represents the one-minute period of emotional excitement; the thick dash-line, the average of the nine cases.

in carbon-monoxide poisoning, or in very vigorous muscular exercise, the spleen promptly contracts and discharges its content into the general blood-stream (3). Thus within a few minutes after exertion has started, there may be an increase of the red corpuscles in circulation amounting to as high as 25 per cent or more (16). (Fig. 39.) These corpuscles like those previously in currency are sent through the

vascular circuit at the greater speed resulting from the high arterial pressure. Their efficacy as carriers, therefore, is to be multiplied by the faster rate of flow which prevails.

In surveying this group of changes directed towards the maintenance of a proper oxygen tension in the tissues one notes that at every point the interofective service of the sympathetic division is at work. It causes constriction of the splanchnic vessels, it accelerates the heart, and it brings about the contraction of the spleen. Since the red blood-corpuscles are not only instrumental in carrying oxygen from the lungs to the tissues but also in carrying carbon-dioxide from the tissues to the lungs, these mechanisms which have been considered in relation to oxygen, are also effective in preventing the development of a harmful acid reaction in the laboring muscles. It is evident that the interofective service of the sympathetic system plays a most important rôle with respect to the homeostasis of both the oxygen supply to the tissues and the acid-base relationship in the blood.

5. *Comparison of Effects of Physical and Emotional Activity*

The rôle of the sympathetic division of the autonomic system has been illustrated as it operates during the performance of muscular work. It is a matter of interest that all of the changes mentioned,—the liberation of sugar from the liver, the pouring out of sweat, the dilatation of the bronchioles, the contraction of the splanchnic area, the acceleration of the heart, and the discharge of corpuscles from the spleen into the general circulation (Fig. 39),—occur also in emotional excitement (15). As the author has already pointed out elsewhere (11), the association of these changes with such strong emotions as fear and rage, lends strong support to the idea that emotional states are anticipatory of action, for every one of these changes renders the organism in which they occur more capable of supreme and prolonged struggle.

FUNCTIONAL DIVISIONS OF THE AUTONOMIC NERVOUS SYSTEM

In 1914 the author (9) called attention to a general division of functions between the cranial portion of the autonomic system and the thoracicolumbar or sympathetic portion. The cranial portion appears to be conservative and upbuilding in its effects. The third nerve, for example, protects the retina against too bright light by constricting the pupil. The vagus holds the heart in check when there is no need

for rapid beating; the seventh and ninth cranial nerves cause secretion of saliva favorable for the ingestion of food and the digestion of starches in the stomach, and the tenth, the vagus, induces a flow of gastric and of pancreatic juice and establishes and maintains tone in the alimentary tract. Furthermore, through action on the pancreas the vagus, by liberating insulin, favors the storage of glycogen in the liver (7). All these processes may be summed up as protective and conservative,—the cranial autonomic division is concerned with establishing the bodily reserves. It is known from physiological tests that when an organ is innervated by both the cranial and the sympathetic divisions of the autonomic system the effects of stimulation are as a rule opposed. For example, the vagi (of the cranial division) slow the heart, the accelerators (of the sympathetic division) make it beat faster; so likewise, there is opposite action on the iris, the blood-vessels of the salivary glands, the stomach and intestines, and other structures. Since the sympathetic is thus antagonistic to the cranial, it is to be expected that when it is brought into action it will stop the conservative, constructive processes of the cranial division. So it does. It temporarily abolishes the motions and secretions of the digestive organs, it greatly accelerates the heart, it widely dilates the pupils. In the main when the sympathetic division induces these changes it also acts to mobilize the reserves which are needed for the proper and efficient functioning of the exterofective system and for the maintenance of a steady state whenever the activities of the exterofective system tend to alter the homeostasis of the fluid-matrix of the body.

Total inactivity of the exterofective system may be considered as a basal state for the organism, i.e., a condition for minimal functioning of both the exterofective and the interofective systems. Whenever the exterofective system becomes active there is produced an internal disturbance, or there tends to be produced an internal disturbance, and associated therewith the basal interofective function is increased in order to maintain homeostasis.

It should be clear from the foregoing considerations that if the organism is maintained in a fairly constant basal condition, i.e., if there is not marked disturbance of the internal environment because of response to external stimuli, there is relatively little need for the functioning of the interofective mechanisms. This in fact has proved

to be the case. As Dr. Robert M. Moore says,[2] it has been possible to keep animals in the quiet circumstances of the laboratory for many months with the sympathetic system entirely removed from them. None of the adaptations which occur in the normal animal occur to a complete degree in these animals and in some instances there is total failure of adjustment. It seems probable that although these animals can live normally in the sheltered conditions of the laboratory, they would not be able to make their way in the outer world.

Much of the work done at the Harvard Physiological Laboratory for many years has been related to the general theory of the emergency function of the sympathico-adrenal mechanism. When first conceived, the emergency theory was applied solely to situations which give rise to strong emotional states. The development of the idea that the sympathico-adrenal mechanism is concerned with the maintenance of homeostasis, that it acts reciprocally with the exterofective system to prevent marked disturbances of the internal environment is not a fundamental modification of the emergency theory. As indicated above, if emergencies do not arise, indeed, if reactions to the outer world do not occur, the sympathetico-adrenal system is not a necessity. It plays its normal rôle, however, not only in emergencies of a grave character, but also in the minor adjustments of the organism required by responses to the environment.

SUMMARY

The doctrine expounded by Bernard (5), that the living parts of the body exist in an internal environment, or fluid-matrix, is reviewed.

The importance of constancy (or homeostasis) of the matrix for continuous efficient action is emphasized.

The fact is pointed out that every response to a situation in the external environment is associated with disturbance in the internal environment. For constancy of the fluid-matrix, therefore, every move in relation to the outer world must be attended by a rectifying process in the inner world of the organism.

Illustrations are given to show that the chief agency for the rectifying process is the sympathetic division of the autonomic system.

The cerebrospinal nervous system, responding to external stimuli, may be called the *exterofective* system, and the autonomic system,

[2] This volume, p. 386.

affecting the domestic affairs of the interior of the organism, may be called the *interofective* system.

When the activity of the exterofective system disturbs the fluid-matrix of the body it is the function of the sympathetic division to maintain homeostasis by its interofective functions.

It is pointed out that this concept does not contravene the theory of the emergency service of the sympathetic or sympathico-adrenal system; rather, it is an extension of that theory from a restricted relation to major disturbances to a general relation to minor disturbances of the organism.

DISCUSSION

The following questions submitted to Dr. Cannon before the Commission, together with the answers to them, are here reported verbatim.

Dr. Jelliffe: Mr. President and Gentlemen: In the first place, I think I can say for the gathering here how much we have enjoyed this very lucid, very succinct, very simple, and very straightforward presentation; a presentation of the wisdom of the body that the ancients talked so much about, that wisdom of the body that knows how to run itself independent of conscious cortical control.

As to the choice of the term, which I believe Dr. Cannon said Dr. Timme was partly responsible for, I ask whether "homeostasis" is as good a term as might be used. The Harvard Stadium is certainly very static. There are, however, a great many kinetic things that take place on the inside of it, and whether Dr. Cannon wished to emphasize what might be called stasis, that is, steadiness, stable equilibrium, which really occurs only with death, I question. Might I suggest "homeokinesis," as a football for the discussion. "Exterofective" and "interofective," following the analogies of Sherrington, are also very well chosen. But why not "propriofective"? If we have a "proprioceptive" sensory system, what then corresponds to the "proprioceptive" motor activities? So much then for etiology and nosology. There is one feature of the paper that interests me a great deal,—although I know nothing about physiology. I am seeking information.

Dr. Cannon, if I understand the paper aright, does one thing that I question. I am putting it in this form solely for purposes of explanation on his part. Although what he really wishes to say, I think, is that his studies are an effort to dissect the relative dynamic values of the sympathetic and the parasympathetic parts of the vegetative nervous system, he has more or less used the expressions, "dominated by" and "exclusively utilized by the sympathetic branch," leaving out of consideration the parasympathetic side which is always necessary in a kinetic situation. Maybe the sympathetic is all that is necessary in a static situation, but certainly some statement of what part the parasympathetic is playing, is necessary in the elaboration of a kinetic situation. In Hughlings Jackson's sense, is not Dr. Cannon failing to differentiate between negative and positive symptoms of sympathetic destruction in his one-sided interpretation?

It is maintained by many (Kraus, Zondek, and others) that in the control of the ionic milieu, for instance, the parasympathetic, to a certain extent, controls potassium utilization of the body, whereas the sympathetic controls the calcium utilization. Certainly a relationship between the calcium and the potassium as ambivalent or antagonistic kations is very important for the ionic milieu, or what Dr. Cannon called the fluid-matrix, in which case it seems to me that undue emphasis should not be placed upon the sympathetic side of the vegetative arc unless the parasympathetic side be emphasized as well.

In Dr. Cannon's paper, and in his remarks about what Dr. Moore is going to speak on, he mentioned the denervated heart, and I want to know what a denervated heart is, not so much from the standpoint of physiological technique, but is it possible to have a denervated heart? The myenteric plexuses exist, as I understand, within the heart itself, as a complicated vegetative mechanism, and, therefore, is not the term "denervated," etymologically at least, open to further explanation?

Dr. Cannon also has said that the striated muscles of respiration are not under sympathetic control. Is Dr. Cannon prepared to deny the general conception, now so prevalent, that striated muscle has a sympathetic control?

Will Dr. Cannon enlighten me further concerning his statement that an emotion is the "anticipation of an action." Those of us who have been interested more or less in psychiatric problems and have worked a great deal with emotional states have evolved a great many hypotheses concerning them. One of the most important of these hypotheses, so far as I see it, is that emotion comes to consciousness when there is a conflict between anticipated actions. Fight and flight, if they are completely neutralized, as it were, produced no emotional reaction. And, instead of an emotion's being the anticipation of an action, shall we not perhaps say that an emotion is a register of the conflict in choice between conflicting elements?

There was one other phrase in the paper which was not emphasized but which interested me a good deal. Dr. Cannon spoke of the total inactivity of the exteroceptive system. Did he mean a *total inactivity* of the exteroceptive system? That cannot possibly happen. We are constantly under the influence of gravity. It influences every electron of our body. We are constantly under the influence of heat and light, to say nothing possibly of our motion in space, Milliken's rays and other unknown things. Therefore, the exteroceptive system is constantly operating and there can be no such thing as its "total inactivity."

Only one further word and that concerns itself, it seems to me, with a problem which interests me a great deal, and I would question Dr. Cannon as to his slant upon it. Insofar as this wisdom of the body, expressed psychologically, may be said to be the result chiefly of unconscious activities, and since these unconscious activities are going on all the time; insofar as thoughts, ideas, conceptions and all kinds of emotional factors in life are constantly playing upon and within the body,—is there not a constant demand for this homeostatic or homeokinetic adjustment?

If a certain distortion occurs in the unconscious material and a prevalent demand therefore takes place, either upon the sympathetic or the parasympathetic branch, is it not possible that definite organic, i. e., structural changes, can take place in the body? And are not these some of the most fundamental of the things that lie behind what we call diseases of the viscera or internal medical diseases?

Dr. Cannon: There are a number of points which Dr. Jelliffe has touched upon to which I should like to respond by demanding proof.

First of all, I should like to know what proof he has that the potassium content or the calcium content of the blood is disturbed by exterofective activity.

Dr. Jelliffe: I said I did not know anything about physiology. I can refer you to Professor F. Kraus and Professor Zondek and I can mention fifty others, all of whom say that they have proved it.

Dr. Cannon: In such activity as takes place in a 100-yard dash?

Dr. Jelliffe: Yes.

Dr. Cannon: Have they studied the 100-yard dash?

Dr. Jelliffe: I will not say precisely the 100-yard dash. It might have been 100 metres, you know.

Dr. Cannon: I do not want to emphasize the total inactivity of the exterofective system. One could dispute for a long time about "total." When one is lying flat on his back and has lain thus for half an hour, as one does before a metabolism determination is made, the effect of gravity on the body is not anything that puts the body to any stress, in my opinion; and the only activity which the individual engages in which involves skeletal muscle, has to do with the muscles of respiration, and he is very likely to be unconscious of their activity.

This state of approximately total inactivity is a standard condition which you are all well aware of and it is this state which I had reference to when I spoke of it as a basal condition, a basal condition in which the interofective system is likewise in a basal state of quiescence.

Again, the question arises as to what effect the Milliken-rays have on the body. Does anyone know anything about that? I take the suggestion with interest but I do not believe there is any proof that they have anything to do with our organism.

A question was raised as to the denervated heart. That is a shorthand expression and I attempted to define it by saying that it was a heart completely disconnected from the central nervous system. So far as the histologists tell us, there is no "myenteric" plexus in the heart. That is a plexus which is connected with the *enteron*, the gastro-intestinal canal. There are the outlying neurones of the vagus, of course, which still remain in the heart, and we have evidence that under certain circumstances they may become active, but when they are disconnected from the central nervous system they can have no message from that system; only thermal and chemical changes in the blood-stream can possibly affect them, and usually they are not affected. In any case, the influence which they would have would be to slow the heart, and all of the responses which we have studied have resulted in an acceleration; they are, therefore, not to be confused at all with the activity of the vagus neurones.

The question was raised about an emotion's being an anticipation of an action. I was careful, or at least I tried to be careful, not to generalize. The emotions

which I referred to were the major emotions of fear and rage. Those emotions are related, as has been recognized for many years, with certain instincts; the emotion of fear, associated with the instinct to escape, to run away, get out of danger; the emotion of rage or aggressive feeling, associated with the instinct to attack. And when one runs and is pursued, or when one attacks and is met by a counterattack, use is likely to be made of the great muscles of the body in what is, perhaps, a supreme and final struggle for one or the other of the contestants. The changes that I have indicated are directed in a preparatory way toward making the organism more effective as an active machine.

The question that Dr. Jelliffe has posed, however, is, I think, of great interest, at least psychologically: Can one have an emotion without uncertainty, without a conflict? I believe that one can be frightened while he is running. He can be enraged while he is attacking. I do not believe that these emotions merely prevail before one gets into action. Certainly, so far as the physiological manifestations are concerned, one sees in lower animals before any attack is made, before any move is made, many of the signs of sympathetic action which from a physiological point of view constitute what we call an emotion. A dog comes into a room while a cat is sitting on the observer's lap and before the cat makes a motion the tail-hairs will be erected, the eyes will be dilated, and there will be an increased heart-rate. These are the physiological responses, at least, which we associate with the emotion, and the animal has not gone into action at all. The same phenomena continue, however, only to a greater degree, when the animal goes into action. It seems to me that the fact that there is at least the physiological aspect of the emotion continuing after the animal becomes responsive to the danger, is indicative that the same process continues after the response starts.

I am very grateful to Dr. Jelliffe for his suggestions about homeostasis and homeokinesis. "Homeostasis" was selected because "stasis" means *condition* as well as stagnation, and because the word resembles "homeothermia," a well-known physiological term designating the relative constancy of the body-temperature. And "interofective" was chosen as being the opposite of "exterofective," directed internally rather than externally; "propriofective" might be more appropriate but it would not call attention to the contrasted effects.

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CHAPTER X

SOMATIC AND VISCERAL CONNECTIONS OF THE DIENCEPHALON[1]

G. CARL HUBER, M.D., AND ELIZABETH C. CROSBY, PH.D.

INTRODUCTION

THE diencephalon, like all other subdivisions of the nervous system, is arbitrarily delimited, and contains within its area a series of centres associated with various functions. These centres are not only interrelated with each other, but they are intimately related with the lower and higher segments of the nervous system. Thus the degree of differentiation of the diencephalon in any form, is in direct relation to the extent of the development of the peripheral nervous system and the degree of differentiation of the spinal, bulbar and pontile centres. Moreover, the possible complexity of the striatal and cortical centres is limited and determined by the complexity of the diencephalon.

A study of the phylogenetic development of the nervous system reveals a gradual increase in the longitudinal conduction pathways and a progressive differentiation through the whole extent of the nervous system, which at certain stages may involve more particularly a single segment, but which must of necessity, because of the various paths, affect to some degree all of the subdivisions. The behavior of the more primitive types of vertebrates is more stereotyped and is concerned largely with relatively direct responses to stimulation. Gradually, as the vertebrate scale is ascended, and coincident with the development of longitudinal conduction paths within the central nervous system and the specialization of nerve-centres, including those of the tectum, forebrain and diencephalon, the response becomes more variable and is capable of much greater delay, as is to be seen in the behavior of mammals, and particularly of primates and man.

In this progressive development the diencephalon plays an impor-

[1] From the Laboratory of Comparative Neurology, Department of Anatomy, University of Michigan.

tant rôle. This brain segment is often referred to as if its only function were that of a ganglionic internode, a place of synapse for impulses passing to the cortex. There is, however, little doubt that, with the exception of the olfactory impulses, the vast majority of the nerve-impulses, which attain cortical centres, do so only after a relay in the dorsal part of the diencephalon. The very presence of these synapses raises the question of localization and interrelation within the diencephalic centres, and stresses the importance and the undoubted existence of modifications of the impulses within these centres. The lack of pure sensations in normal human psychology is to be expected in the absence of such anatomic connections and specific localization within the diencephalon as would provide the mechanism for such sensations. Nevertheless, just as the dorsal part of the diencephalon is a means of entrance to the striatal and cortical centres, so other portions of this brain segment are equally important regions of synapse for efferent fibers from the cortex and the striatum to the lower centres. In addition to these functions, the diencephalon comprises a reflex centre for proprioceptive, exteroceptive and interoceptive impulses, and a conscious centre for unlocalized pain. A further important series of relations of which little is known in higher forms, aside from the auditory and optic centres, are those of the tectodiencephalic and diencephalotegmental connections.

The thalamus provides for the affective tone of impulses, and is a primary centre involved in various types of emotional expression. Irritation or injury of its various regions leads to chorea, tremor and automatic screaming and crying. Injury or irritation of the region may change the whole affective attitude of a person. Normally, this centre gives the emotional content to a given response. The work of Head and Holmes (19) indicates that the thalamus is closely connected with affective experience and with the whole range of pleasurable and painful qualities, which are undisturbed when lesions are confined to cortical centres alone. Tilney and Riley (53) have emphasized particularly the relation of these primitive emotional qualities to the development of personality and behavior. Pain apparently comes into consciousness in the thalamus, as is evidenced in the work of Head and Holmes. The question of pleasure and pain from the neurologic standpoint, and the general functions of the diencephalon have been discussed by Herrick (23, 24). The work of von Bechterew (3), Strümpell (52), von Monakow (38), Déjerine (11), Head and

Holmes (19), Jelliffe and White (31) and others, may be consulted for further accounts of the functional activity of the thalamus as exhibited in clinical cases.

To a study of the diencephalon there are many avenues of approach. Attention may be drawn to the following aspects: clinical studies, which have contributed fundamentally to a knowledge of the diencephalon; experimental observations, which have widened the horizon and indicated regions deserving of further study; anatomic descriptions, which have given the general nuclear pattern and certain fiber connections; and the comparative neurologic approach, which has contributed much to an understanding of the factors involved in the progressive development of the diencephalon and has consequently revealed the significance of the gradual differentiation of its various parts. The following brief survey of the diencephalon is based on a comparative neurologic study of this brain segment, supplemented by a study of the literature. To any one familiar with the field it is unnecessary to state that the limits set for this contribution preclude a full consideration of the literature involved, so that only such relations and connections have been emphasized as appear to have special significance for the specific functional activities of this region. It may be emphasized that all adequate physiologic experimentation must have its basis in a thorough knowledge of the normal anatomy of the form on which the experiment is performed.

SUBDIVISIONS OF THE DIENCEPHALON

In the following account, the diencephalon has been divided into epithalamus, hypothalamus and thalamus, the latter being secondarily divided into a dorsal and a ventral portion. The geniculate bodies, which are sometimes classified as metathalamus, are here regarded as part of the dorsal thalamus. The ventral thalamus includes those efferent centres below the sulcus medius, the greater part of which are grouped in ordinary terminology under the term subthalamic centres. This subdivision of the diencephalon is not in agreement with the B. N. A. classification, but is to be found with various modifications in contributions based on comparative neurologic studies. These subdivisions, unlike those of the B. N. A., have their basis in the phylogenetic and the functional development of this region. The major diencephalic subdivisions may be summarized as follows:

1. Epithalamus
2. Thalamus
   (*a*) Dorsal thalamus, including geniculates
   (*b*) Ventral thalamus (subthalamus)
3. Hypothalamus

In the main, the epithalamus and hypothalamus are respectively olfactosomatic and olfactovisceral correlation centres for conscious and reflex responses to olfactory stimulations. The dorsal thalamus is particularly concerned with the reception of exteroceptive and proprioceptive impulses (in most cases after synapse in lower centres), and with their transmission either to the striatum and cortex of the forebrain, or directly to the efferent centres. The ventral thalamus is on the efferent side of the arc. It conducts impulses received from the dorsal thalamus, from the lenticular nucleus, and, to some extent, from the motor cortex to the efferent centres of the midbrain, pons, medulla and spinal cord. Epithalamic and hypothalamic centres, therefore, are concerned primarily with the reception of visceral or interoceptive impulses and with their correlation and discharge to the appropriate somatic and visceral efferent centres. The dorsal and ventral thalami are concerned primarily, although not exclusively, with a similar correlation of exteroceptive and proprioceptive impulses and with their discharge to the proper centres.

Epithalamus and Hypothalamus

These two diencephalic subdivisions may be considered together with profit, by reason of certain parallelisms in structural arrangement and functional activity. This is well illustrated in the following outline, in which epithalamus and hypothalamus are each divided into endocrine, olfactory and non-olfactory portions.

Epithalamus

1. Endocrine: Epiphysis and chorioid plexus of the third ventricle
2. Non-olfactory portion: Posterior commissure
3. Olfactosomatic correlation centres: Habenular nuclei, habenular commissure and stria medullaris

Hypothalamus

4. Endocrine: Hypophysis (pars neuralis of neural tube genesis, the remainder from oral cavity)
5. Non-olfactory portion: Pars optica hypothalami, mainly chiasm and supra-optic commissure
6. Olfactovisceral correlation centres: Corporal mammillaria, tuber cinereum and associated hypothalamic gray matter

For the present the glands of internal secretion will not be discussed. However, it is worthy of note that here, as elsewhere in the nervous system, regions not directly concerned with the conduction of nerve-impulses frequently acquire secondarily secretory function. The non-olfactory components of the epithalamus and hypothalamus are made up largely of fiber-bundles, decussating and commissural in character, which in the main connect regions outside of the epithalamic and hypothalamic areas.

Non-olfactory components. The posterior commissure, the non-olfactory component of the epithalamus, lies at the boundary line between the diencephalon and mesencephalon and is sometimes regarded as belonging entirely to the latter segment. In reptiles and birds, in which the pretectal and tectal centres are highly developed, this commissure is correspondingly large. In these forms it consists of two major divisions, a dorsal division providing commissural connections between the optic tecta and a ventral division carrying commissural and decussating fibers between pretectal and inferior collicular (corpus posticum) centres and fibers from associated nuclei of the commissure. Furthermore, in reptiles it has been demonstrated that this commissure transmits fibers arising in the nucleus of the median longitudinal fasciculus of one side and passing to the corresponding fasciculus of the other side. In mammals, particularly in higher mammals and in man, the posterior commissure is greatly reduced. In these forms it is known to interconnect the superior colliculi of the two sides. Fibers which course in it to the posterior thalamic regions are probably the remnants of the phylogenetically old pretectal connections. There is reason to believe that in mammals, as in lower forms, fibers from the nucleus of the median longitudinal fasciculus, cross to the contralateral fasciculus by way of this commissure; but this theory needs confirmation in regard to the higher mammals and man. So far as present knowledge goes, there is no trace of the inferior collicular connections for reptiles and birds. All the evidence indicates that the posterior commissure is a dependency of the tectal, pretectal and subtectal regions of the vertebrate brain, and that it increases or decreases as these areas increase or decrease.

The optic chiasm, one of the main fiber-bundles of the non-olfactory portion of the hypothalamus, is composed of decussating and non-decussating fibers extending between the retina and the dorsal thala-

mus, the tectum and tegmentum of the midbrain. This important system of fiber bundles will be given further consideration in the discussion of the optic portion of the dorsal thalamus.

Crossing in the chiasmal ridge at the level of the optic decussation and immediately behind it are found the supra-optic or postoptic commissural systems. These consist of three main portions, which are capable of still further subdivision and are variously designated in the literature. The division most ventrally placed and in mammals, where it is usually medullated, frequently indistinguishable from the optic tract, is Gudden's commissure. This is also known as the ventral supra-optic or ventral postoptic commissure. It connects the medial geniculate bodies of the two sides and, to some extent, the inferior colliculi. Comparative neurologists (45) have demonstrated this fiber system in amphibians, reptiles, birds and mammals (Fig. 40). Larsell (34) described a commissura transversa in the frog, which he considered comparable to the mammalian commissure of Gudden.

The second of the supra-optic or postoptic commissural systems is most frequently designated as Meynert's commissure. It is a relatively complex system of fibers with no single nucleus of origin and no single nucleus of termination. The postoptic system, described by Herrick (22) for Necturus, is probably the forerunner of both Gudden's and Meynert's commissures as found in higher forms. It may contain representatives of Ganser's as well. Herrick showed that the postoptic system is complex in Urodeles. It consists of two main divisions. The first, tractus tectothalamicus and hypothalamicus cruciatus, has anterior and posterior divisions which are related to areas homologous with the mammalian superior colliculi. These distribute fibers, after decussation, to the ventral thalamus, hypothalamus and the nucleus of the tuberculum posterius. Certain unmedullated fibers from the superior colliculus, after decussation, appear to distribute to the pars optica thalami. The second division, tractus thalamohypothalamicus and peduncularis cruciatus, arises in the pars dorsalis thalami, and after decussation terminates in the ventral part of the thalamus and the region of the cerebral peduncle. The authors' own observations on reptiles confirm in a general way these observations on amphibians, but show in Meynert's commissure first, a significant increase in the intertectal and tectothalamic fibers, associated with the presence of a more highly developed reptilian tectum; and second, an intermingling and synaptic relation of this

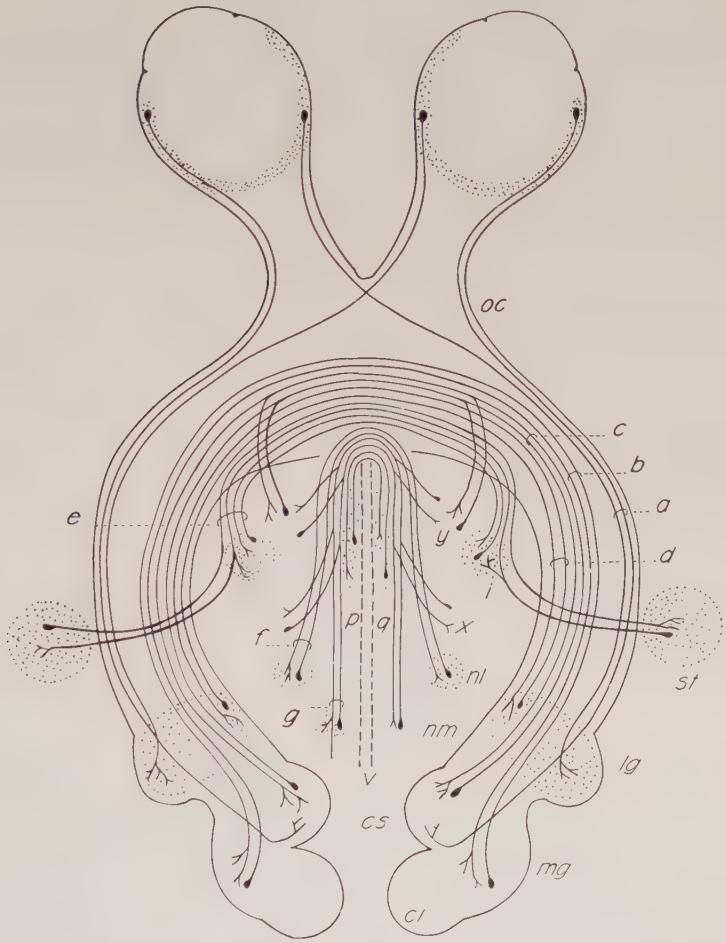

FIG. 40. Supra-optic systems: *a*, optic fibers; *b*, Gudden's commissure; *c*, superior collicular component of Meynert's commissure; *ci*, inferior colliculus; *cs*, superior colliculus; *d*, intergeniculate fibers; *e*, striatal component of Meynert's commissure; *f*, subthalamic component of Forel's commissure; *g*, median longitudinal fascicular component of Ganser's commissure; *i*, subthalamic areas; *lg*, lateral geniculate; *mg*, median geniculate; *nl*, nucleus Luysi or subthalamic nucleus; *nm*, nucleus median longitudinal fasciculus; *oc*, optic chiasm; *pg*, periventricular gray matter and fibers; *st*, striatum; *v*, ventricle; *x* and *y*, hypothalamic and ventral thalamic gray matter. Forel's commissure is the supramammillary commissure.

system with the forebrain paths. In birds, the authors' own (28) observations confirm and extend earlier statements with regard to this commissure. They indicate, as various neurologists have contended, that in avian forms there are fibers from the striatal region of one hemisphere to the homolateral and contralateral ventral thalamus, and to the contralateral striatum. However, the system shows great similarity to the fibers in reptiles. In higher mammals, with the relative reduction of the tectum as compared with that of reptiles and birds and with the reduction of the striatum as contrasted with that of avian forms, Meynert's commissure forms a proportionately less prominent fiber-bundle. Yet in mammals it is still a complex system with all of the components which it has acquired in phylogeny. Certain of its more prominent bundles are illustrated in Figure 40 and may be listed as follows: *c*, tectal fibers associating the superior colliculus with the contralateral ventral thalamus; *d*, intergeniculate fibers which pass from one lateral geniculate to the other and are probably not present in all mammals; *e*, fibers connecting one lenticular nucleus with that of the other side and with subthalamic regions. This fiber-system has been better identified in submammalian forms, and it is probable that there are present various other significant connections in higher forms not included in this list. As regards its components, there is no general agreement in the literature. Some workers, among them Wallenberg (59–62), regard it as carrying decussating lemnisci fibers; certain writers have confirmed (Tsai (55, 56)) and others denied (Déjerine (11)) its relation to subthalamic nuclei. Foix and Nicolesco (15), in their comprehensive recent account of the thalamus, listed, with other connections of Meynert's commissure, a connection with the substantia innominata of Reichert. It is evident that further investigation is required to give an adequate understanding of this system, in spite of the great amount of work which has been done upon it.

The third member of the supra-optic commissural system is Ganser's commissure, in part at least also known as fibrae ansulatae. In this commissure course fibers which interconnect the subthalamic or ventral thalamic regions of the two sides, as has been shown by Tsai (55, 56) for marsupials and by Gurdjian (18) for rodents. The periventricular gray matter in the region caudal to the chiasm is likewise connected by fibers of this commissure. In it course also fibers which arise in the nucleus of the median longitudinal fasciculus

of one side and pass to the contralateral nucleus, and possibly directly to the median longitudinal fasciculus, of the other side. The fibers to the nucleus of the fasciculus were described for Varanus by Beccari (2) and are evident in the authors' material of *Alligator mississippiensis* (Huber and Crosby (27)). They believe them to be present in birds and mammals. The components of Ganser's commissure are shown in Figure 40, *x* and *y*, indicating the subthalamic component; *g*, the median longitudinal fasciculus component; and *pg*, the periventricular component.

Olfactory components. The habenula of the epithalamus and the mammillary body of the hypothalamus show certain resemblances in structure and fiber connections which are emphasized in the accompanying outline. The following account is based on avian and particularly on general mammalian relations; especial points in human beings will be stressed.

- Epithalamus (olfacto-somatic correlation centre)
  - Into habenula
    - Corticohabenular
    - Olfactohabenular (stria medullaris)
    - Thalamohabenular
    - Tectohabenular
  - Out of habenula
    - Habenulodiencephalic (thalamic)
    - Habenulotegmental (dorsal tegmental nucleus)
    - Habenulopeduncular (interpeduncular nucleus)
- Hypothalamus (olfactovisceral correlation centre)
  - Into mammillary body
    - Corticomammillary (fornix)
    - Olfactomammillary (anterior perforated space)
    - Cineromammillary (hypothalamomammillary)
    - Mammillohypothalamic (tuber cinereum)
    - Mammillary peduncle
  - Out of mammillary body
    - Mammillothalamic (Vicq d'Azyr)
    - Mammillotegmental (dorsal tegmental nucleus)
    - Mammillopeduncular (interpeduncular nucleus)

The habenula consists in birds and mammals, including man, of two nuclei: an internal one containing medium sized, rather closely packed neurones, and an external one composed usually of more scattered cells. In the majority of mammals the mammillary body

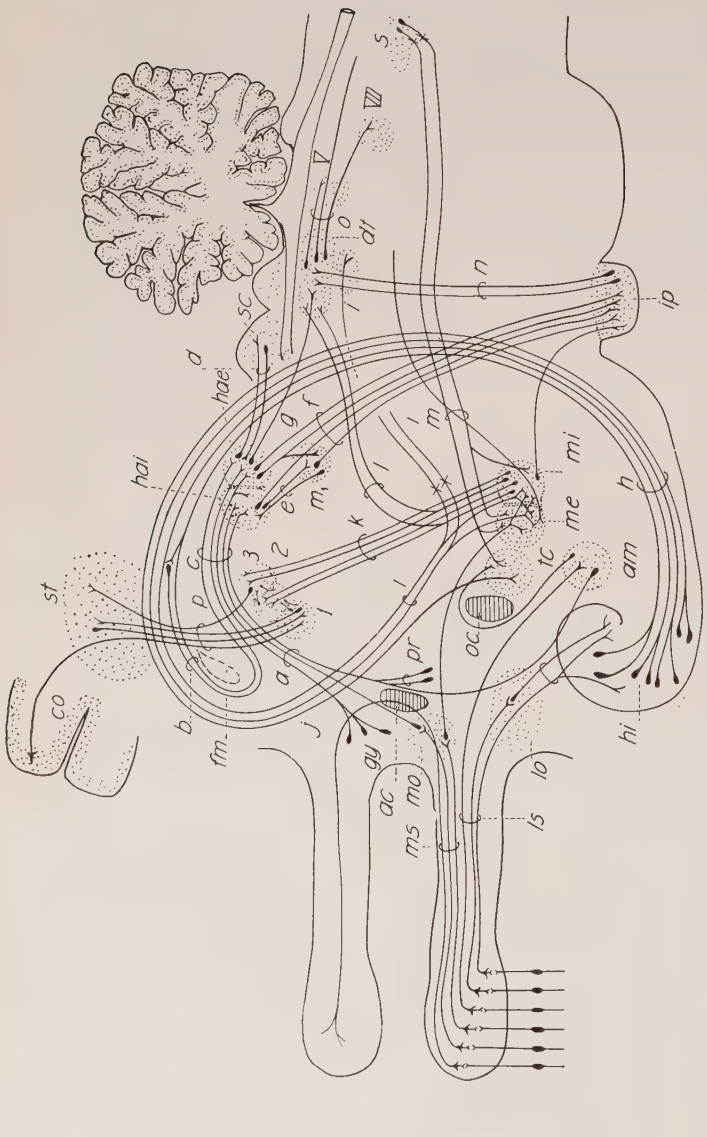

FIG. 41. Olfactory connections of the diencephalon: *a*, olfactohabenular fibers; *ac*, anterior commissure; *am*, amygdaloid nucleus; *b*, septohabenular and cortico habenular tract; *c*, stria medullaris; *co*, cortex; *d*, tectohabenular and habenulotectal fibers; *dl*, dorsal tegmental nucleus; *e*, habenulodiencephalic and thalamohabenular fibers; *f*, habenulopeduncular fibers; *fm*, foramen of Monro; *g*, habenulotegmental fibers; *gy*, gyrus subcallosus; *h*, fimbria; *hae*, external habenular nucleus; *hai*, internal habenular nucleus; *hi*, hippocampus; *i*, fornix; *ip*, interpeduncular nucleus; *j*, corticohypothalamic (and septohypothalamic) fibers; *k*, mammillothalamic fibers; *l*, mammillotegmental fibers; *lo*, lateral olfactory area; *ls*, lateral olfactory stria; *m*, mammillary peduncle; m_1, nucleus of Meynert's habenulopeduncular tract; *me*, external mammillary nucleus; *mi*, internal mammillary nucleus; *mo*, medial olfactory area; *m5*, medial olfactory stria; *n*, pedunculotegmental fibers; *o*, dorsal longitudinal fasciculus of Schultze; *oc*, optic chiasm; *pr*, pre-optic area; *s*, bulbar centres; *sc*, superior colliculus; *st*, striatum; *tc*, tuber cinereum; *V*, motor nucleus of the fifth nerve; *VII*, motor

likewise has an internal and an external nucleus. In man the latter is greatly reduced; it is more or less fused with the so-called mammillo-infundibular nucleus and it is sometimes regarded as absent. Olfactory impulses entering the olfactory bulb by way of neuraxes from the olfactory epithelium of the nasal cavity are distributed, after synapse, as interbulbar fibers to the bulb of the opposite side (Fig. 41 *a*), and to the medial olfactory area (including gyrus subcallosus) and the lateral olfactory area of the anterior perforated space. From the medial olfactory area, the gyrus subcallosus, the pre-optic area and the amygdaloid nucleus neurones of the next order send their neuraxes to the habenula, all entering it by way of the stria medullaris and appearing to be distributed chiefly to its internal nucleus. Other fibers, either with or without a synapse in the medial olfactory area, pass to the septum or to the gray stria of Lancisi which overlie the corpus callosum and are regarded as the forward continuation of the hippocampus. They are not illustrated in the figure since the primary consideration here is the diencephalic relations. Olfactory impulses from the bulb reach the amygdaloid nucleus and the hippocampus in the temporal lobe region, either directly from the bulb or after a synapse in the lateral olfactory area. From the hippocampus they pass by way of the fimbria and posterior pillars and body of the fornix to the level of the interventricular foramen. In their course along the septum, they are in synaptic relations with neurones of the area and are joined by fibers from it. At the level of the foramen, fibers of the bundle swing caudalwards to reach the habenula by way of the stria medullaris (Fig. 41 *c*). This component of the stria medullaris carries septohabenular and, it is also believed corticohabenular fibers. The presence of a corticohabenular system has been denied by certain other observers (Ramón y Cajal (9)). The corticohabenular and septohabenular components are particularly related to the external nucleus. Further work needs to be done on the details of the termination of the stria medullaris components within the habenula. After the entrance of the corticohabenular and the septohabenular systems into the stria medullaris, the remaining and larger portion of the fornix system swings ventrocaudad to the hypothalamic region as the anterior pillars (Fig. 41 *i*). A part of the fibers, corticohypothalamic and septohypothalamic in nature, according to Gurdjian (18) are distributed to the hypothalamic regions in front of the mammillary body. A varying proportion of the fibers, depending upon the mammal

studied, are distributed to the internal and external nuclei of the mammillary body. Still other fibers decussate in the supramammillary decussation and course caudad and dorsad into the tegmental region of the midbrain, where their final distribution is as yet unknown. Many observers have contributed to the knowledge of the fornix system in mammals, among whom may be especially mentioned Edinger (12), Edinger and Wallenberg (13), Wallenberg (59–62) and Cajal (9). Connections have also been described from the amygdaloid nucleus to the hypothalamus; these will be considered later. Thus the habenula and the mammillary nuclei receive impulses from both basal and cortical olfactory centres.

In birds, the external habenular nucleus is connected with the tectum by a fiber-bundle which possibly carries impulses in both directions, thus providing habenulotectal and tectohabenular connections. By means of the latter, optic and, to a certain degree, other exteroceptive impulses may be carried forward to the habenula. Likewise, the more posterior portion of the dorsal thalamus, corresponding possibly to the nucleus along the tract in mammals, is in synaptic relation with the internal habenular nucleus by way of habenulodiencephalic and thalamohabenular fibers. The latter system, which is non-medullated in birds, but which is prominent there even in the presence of a relatively small habenula, has in all probability representatives in mammals. Edinger (12) described a habenulodiencephalic path. Whether the mammalian nucleus parafascicularis (Fig 41 *m*) or, as it is sometimes known, the nucleus of Meynert's tract, is the homologue of this avian nucleus still requires demonstration. The thalamohabenular fibers, through the interrelalation of their nucleus with other dorsal thalamic centres, are able to carry to the habenula exteroceptive impulses, perhaps particularly of pain and temperature, possibly of tactile sensibility as well. Thus this centre becomes an olfactosomatic correlation centre. The thalamohabenular and habenulodiencephalic fibers are associated with the habenulopeduncular system or, as it is frequently termed, the tractus retroflexus of Meynert. This bundle is phylogenetically old, being well developed in many lower forms. It is relatively large even in avian forms where the olfactory system is not highly developed and the stria medullaris is small, indicating that it is concerned in the discharge of other impulses as well as the olfactory. In the dove it consists of two bundles, a medullated one arising from the external

and an unmedullated one from the internal habenular nucleus. The medullated bundle carries with it, on the lateral side, the tectohabenular (and habenulotectal?) fibers. Some few of its fibers terminate, in relation with the associated nucleus of the habenulopeduncular tract, as habenothalamic fibers, but the greater number swing ventromediad to pass to the interpeduncular nucleus. The medial habenulopeduncular tract carries with it many habenulodiencephalic and thalamohabenular fibers, which enter into synapse in the nucleus of the tract. The main bundle, joined by fibers arising in this associated nucleus, courses ventrad and likewise enters the interpeduncular nucleus (Fig. 41 *f* and *ip*). The nucleus of the habenulopeduncular tract is situated in the dorsal thalamus. Probably it is not the homologue of the mammalian nucleus parafascicularis (d'Hollander (26)) or nucleus of the tract of Meynert. The details of the connections in birds have been discussed by the authors in an account of the avian forebrain and diencephalon (28).

The detailed relations of the habenulopeduncular tract are somewhat less understood for mammals. Both internal and external habenular nuclei are known to contribute fibers to it. As it passes through the dorsal thalamus near the posterior end of the medial nucleus, it is partly surrounded by the parafascicular nucleus (nucleus of the tract of Meynert). The majority of investigators at least fail to note whether or not the tract is in synaptic relation with this nucleus. The authors are inclined to believe that there is a synapse in the gray matter of the region and, in Figure 41 m_1, have suggested the possibility of such a relation. The curious terminations of the habenulopeduncular tract within the interpeduncular nucleus have been noted by various observers and have been particularly well described by Cajal (9) whose figures show the decussation and looping back of these fiber-bundles within the nucleus in question. In many animals a small fiber-tract—tractus habenulotegmentalis—connects the habenula with the dorsal tegmental region (Fig 41 *d*).

As will be evident from the later discussion, the mammillary nuclei are interconnected with the hypothalamic nuclei. They likewise are in relation with the mammillary peduncle (Fig. 41 *m*). With regard to the origin and the direction of conduction of the fibers of this peduncle, there has been much difference of opinion. It will be possible to quote here only representative points of view. Thus, von Kölliker (33) and Déjerine (11) described it as a descending pathway

from the external mammillary nucleus to the dorsal (von Kölliker), or to both dorsal and ventral (Déjerine) tegmental nuclei. Winkler (65) likewise regarded it as a descending path from the external mammillary nucleus, considering that the fibers joined the medial lemniscus in the midbrain region. Forel (16), Wallenberg (59) and certain others regarded the bundle as one of the constituents of the medial lemniscus, which becomes detached from the main lemnisci system and terminates in the mammillary nuclei. Edinger and Wallenberg (13), however, believed that the bundle is joined by fibers from the tegmental region of the midbrain. Wallenberg (60), and later Edinger and Wallenberg (13), found degenerated fibers in the contralateral mammillary peduncle, as well as in the medial lemniscus, after destruction of the nuclei of the posterior columns (the neighboring gray matter was undoubtedly involved also), so that they believed this peduncle contained, in part, ascending fibers from the contralateral bulbar centres. Cajal (9), who studied the mammillary peduncle in the mouse, rabbit and cat, came to the conclusion that the pathway consists of a principal and of an accessory bundle, of which only the latter is associated with the medial lemniscus. As the bundles swing toward the mammillary body, they become incorporated into the mammillary peduncle, which courses downwards and inwards toward the external mammillary nucleus. According to this observer, the peduncle bifurcates as it passes toward the mammillary body, forming an anterior and a posterior branch. For the details of their distribution reference should be made to the work of Cajal (9). For the present purpose it is sufficient to state that he regarded the mammillary peduncle as an ascending path carrying nerve-impulses to the external and internal mammillary nuclei and to the tuber cinereum cephalad to them. Cajal emphasized that the origin of the fibers was unknown, but suggested as a possibility that they might carry gustatory impulses.

Papez (41, 42), by section of the mammillary peduncle in the rat near its pontile end, produced evidence that it degenerated in an ascending direction and was to be regarded as terminating in the mammillary body. Thus his work was in confirmation of that of Cajal, but in disagreement with that of von Kölliker and Déjerine and, as Papez himself stated, with the results of Schipoff, a student in von Bechterew's (3) laboratory, who studied the tract in the dog. Papez, however, did not ascertain the origin of the bundle.

Negative evidence as to the presence of gustatory fibers in the mammillary peduncle appears to be offered by the recent experimental work of Allen (1) on the cat. In the destruction of all except the extreme cephalic end of the gustatory portion of the nucleus tractus solitarii and of the upper half of the general visceral part of the nucleus of that tract, he did not produce any lesions in the corpora mamillaria or tuber cinereum, although he traced many degenerated fibers to the ventral nucleus of the thalamus. He found minute black granules in the mammillary peduncle and also in the optic tract, but disregarded them because of their size and their presence in all of his Marchi material. Section of the medial lemniscus in the inferior collicular region produced chromatolysis of the cephalic half of the general visceral portion and in the gustatory portion of the nucleus tractus solitarii. Allen's results would appear to indicate that gustatory fibers run in the medial lemniscus or, in his own words, "in adjacent fibers." Since the lesions showing chromatolysis were made at inferior collicular levels, the question as to whether or not adjacent fibers might include the mammillary peduncle, appears justifiable. Allen's evidence as to the presence of gustatory fibers in the medial lemniscus appears convincing, his elimination of the ascending fibers of the system, by way of a mammillary peduncle component of the medial lemniscus to the mammillary body, appears to the authors less convincing and needs further confirmation. It is scarcely necessary to say that the mammillary peduncle is not yet understood and that before final statements can be made, further investigations, preferably of an experimental nature, are essential. The evidence at present would suggest: (*a*) that the mammillary peduncle is ascending in character since the destruction of the mammillary body produces no degeneration within it (Papez (41, 42)); (*b*) that it is composed of two bundles, the principal and accessory bundles of Cajal (9); (*c*) that as yet there is no evidence as to the origin or function of the principal bundle, although various observations suggest that it may be in relation with the tegmental nuclei (Fig. 41 *m*, the upper fiber of the peduncle); (*d*) that the accessory bundle arises at least from the contralateral regions of the bulb at or near the plane of origin of the medial lemniscus, since injuries at that level produce degenerations in the mammillary peduncle of the opposite side (Wallenberg (60)); and (*e*) that its nucleus of origin is probably a secondary or tertiary afferent centre, but that its location is not definitely known

(Fig. 41 *s*, and the two lower fibers of the mammillary peduncle). In lower forms, particularly in fishes (Herrick (21)), gustatory fibers have been traced from the gustatory centres of the medulla forward to a nucleus near the isthmus region, where they enter into synapse. This secondary gustatory nucleus gives rise to fibers which pass to hypothalamic regions. Thus the hypothalamus is an olfactovisceral (gustatory) centre. In higher forms, such as mammals, there is considerable clinical and experimental evidence that the tuber cinereum is concerned with visceral functions. Both it and the mammillary body receive olfactory impulses, and this portion of the brain is again an olfactovisceral correlation centre, although probably not in the same sense as in fishes.

The fibers of the mammillothalamic and mammillotegmental tracts arise, according to Cajal (9), as bifurcations of single neuraxes, from cell-bodies within the mammillary nuclei. The neuraxes pass dorsad and then divide by a Y- or T-shaped division, one prong passing to the mammillotegmental and one to the mammillothalamic tract. Such bifurcating fibers are joined (Gurdjian (18)) by smaller non-dividing fibers which run in the mammillothalamic division of the bundle. According to Cajal, the bundle arises from both mammillary nuclei, while Gurdjian was able to demonstrate its origin only from the internal nucleus. There may be variations in different forms. The mammillotegmental tract terminates in the dorsal tegmental nucleus, the mammillothalamic within the anterior nuclei of the thalamus, particularly its anterior medial nucleus, but to some extent in its anterior ventral and possibly in its anterior dorsalis (with regard to the latter connection there is difference of opinion).

Thus far, impulses have been traced from the habenula and from the mammillary body to the dorsal tegmental nucleus and to the interpeduncular nucleus. From this last cell-mass the impulses are relayed to the dorsal tegmental region by way of the pedunculotegmental tract (Cajal (9), Déjerine (11) and others). The discharge path from the dorsal tegmental nucleus is the dorsal longitudinal fasciculus of Schultze (Déjerine and others), which carried impulses to the motor nuclei of the fifth and seventh nerves, and probably to the general visceral efferent centres of the bulb.

Hypothalamic areas. Along the ventral surface of the brain and the ventral part of the ventricle wall, between the level of the anterior commissure and that of the mammillary body, there is a more or less

continuous sheet of gray matter capable, however, of secondary delimitation into nuclear groups. This whole area comprises the pre-optic and hypothalamic regions. The former belongs to the telencephalon, rather than to the diencephalon, but is so related to the hypothalamic areas that it is best to consider it with them.

There is no general agreement with regard to the nomenclature of the nuclear group. In the pre-optic area the ventricle wall is bordered by a narrow band of periventricular gray matter. This is present in lower forms, such as birds. It is evident in mammals, though the clearness with which it is differentiable varies with different animals. External to the periventricular layer is the medial pre-optic nucleus, and still farther lateralwards the lateral pre-optic centre. These are present in birds and various mammals. In the hypothalamic region, Cajal differentiated a nucleus tangentialis in close relation to the optic fibers, a subventricular nucleus (*noyau sous ventriculaire*), and three nuclei which he regarded as belonging to the tuber cinereum in the strict sense of the word. These nuclei he termed nucleus principalis or anterior, nucleus superior and nucleus posterior. He was able to contribute somewhat to their fiber connections, for he traced into the area of the tuber cinereum some few fibers of the mammillary peduncle; to the anterior nucleus he carried stria terminalis and fibers from the capsule of the mammillary body. Cajal worked on the rabbit, mouse and rat. A more recent account of the hypothalamic region in the rat and considerable detail as to the fiber connections of the various nuclei is to be found in the paper of Gurdjian (18) on the diencephalon. In most essentials his results agreed with those of Cajal. He divided the hypothalamic region into a series of nuclei for the detailed relations of which the original paper should be consulted. In general, his results are as follows: Immediately behind the medial pre-optic area is a poorly defined but relatively large nuclear mass capable probably of secondary divisions, which he terms the anterior hypothalamic area. Ventral to this area is a small nucleus ovidus which is probably the nucleus suprachiasmaticus of certain other observers, and along the optic chiasm is the nucleus tangentialis of Cajal. As the optic fibers disappear from the midline, the nucleus supra-opticus appears in the course of Ganser's commissure. Beginning external to the anterior hypothalamic nucleus and not sharply delimited cephalad from the lateral pre-optic nucleus is the nucleus hypothalamicus lateralis. This scattered cell-mass extends through-

out practically the extent of the hypothalamus, always maintaining its lateral position, in relation to the median forebrain bundle. Immediately caudad to the anterior hypothalamic nucleus and medial to the lateral hypothalamic nucleus, the gray matter of the region differentiates into further nuclear groups, nuclei hypothalamicus ventromedialis, dorsomedialis and posterior. At this level Gurdjian identified a filiform nucleus. These nuclei disappear at some slight distance in front of the mammillary body and the dorsal and ventral premammillary nuclei appear,—the former in relation with the medial hypothalamic area and the latter with the lateral hypothalamic nucleus. Internal to the medial groups of hypothalamic gray matter and lying close to the ventricle are the anterior and posterior periventricular nuclei. Attention is called to Figure 42 in which are diagrammed the hypothalamic nuclei. In this diagram the Gurdjian nomenclature has been followed more nearly than that of any other worker. This choice of terminology has depended partly on the greater personal familiarity of the authors with the results, since the work was done in their laboratory; and partly on its usefulness from the standpoint of the diagram of the more detailed account of the fiber connections of the region. The ventromedial nucleus of Gurdjian is evidently the homologue of the principal nucleus of Cajal. The dorsomedial and posterior nuclei of the former are probably in part the homologues of the superior nucleus of the tuber cinereum of the latter worker, while the dorsal premammillary nucleus at least falls within the posterior nucleus of Cajal. Further homologies of the nuclear masses in these two studies are at present uncertain.

Studies of the hypothalamic region in higher mammals have been made by a number of observers, and excellent accounts of the cyto-architectonic and myelo-architectonic structure in primates, including man, are to be found in the literature. Unfortunately, the majority of these give few, if any, fiber connections, a state of affairs which increases the difficulty of establishing definite homologies and does not contribute to a knowledge of the function of the region, although it adds to a knowledge of its structure. Certain nuclei, however, have been identified by numerous observers; among these are the tangential or perichiasmatic nucleus (Malone (35), Cajal (9), Friedemann (17), Spiegel and Zweig (51) and others), and the basal optic ganglion (Winkler and Potter (65)), the mammillo-infundibular, to some extent the equivalent of the ventral premammillary nucleus (Malone, Gurd-

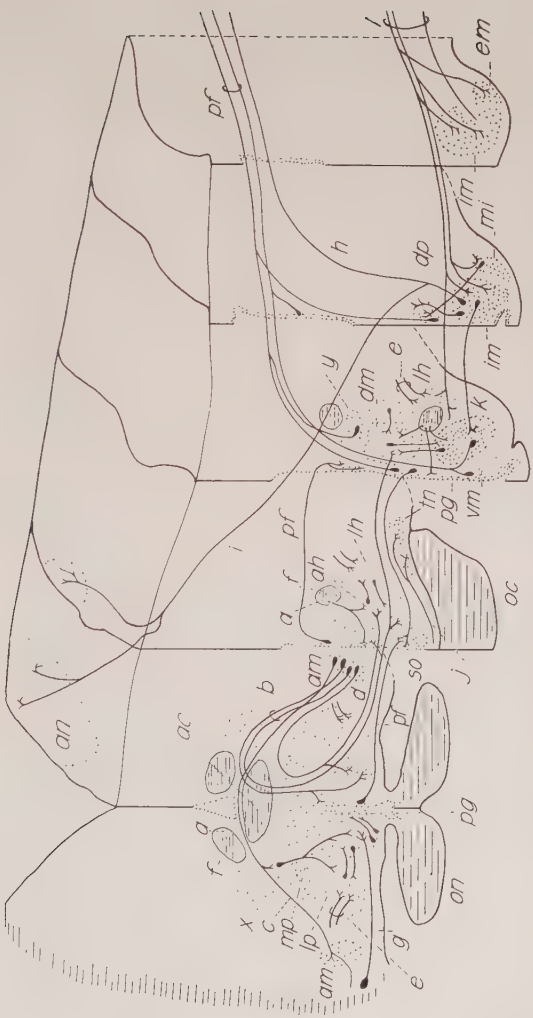

FIG. 42. Fiber connections of the pre-optic area and the tuber cinereum: *a*, corticohypothalamic and septohypothalamic tract; *ac*, anterior commissure; *am*, amygdaloid nucleus; *an*, anterior thalamic nucleus; *b*, supra-optic component of stria terminalis; *c*, commissural component of stria terminalis; *d*, pre-optic component of stria terminalis; *dm*, dorsomedial hypothalamic nucleus; *dp*, dorsal premammillary nucleus; *e*, medial forebrain bundle; *em*, external mammillary nucleus; *f*, fornix; *g*, pyriform lobe and pre-optic connections; *h*, mammillotegmental fibers; *i*, mammillothalamic fibers; *im*, internal mammillary nucleus; *j*, fibers of Meynert's commissure; *k*, mammillohypothalamic fibers; *l*, mammillary peduncle; *lh*, lateral hypothalamic nucleus; *lp*, lateral pre-optic area; *mi*, mammillo-infundibular nucleus; *mp*, medial pre-optic area; *oc*, optic chiasm; *on*, optic nerve; *pg*, periventricular gray matter; *so*, supra-optic nucleus; *tn*, tangential nucleus; *vm*, ventromedial hypothalamic nucleus; *x*, prethalamic nucleus; *y*, posterior hypothalamic nucleus.

jian (18) and others) and the nucleus suprachiasmaticus (Spiegel and Zweig, nucleus ovoidus of Gurdjian). The gray matter of the tuber itself has been variously divided. For a detailed account of the nuclear masses in the region, the original papers should be consulted.

Cajal carried stria terminalis fibers (taenia semicircularis) to the principal and superior, and with lesss certainty to the posterior, nucleus of the tuber. The distribution of the system, as given by Gurdjian, agrees substantially with this, although contributing more in detail. The latter observer carried both pre-optic and supra-optic and supracommissural components of the stria to the nucleus ovoidus and the anterior hypothalamic area, and the supracommissural portion likewise to the ventromedial and dorsomedial hypothalamic areas and to the nucleus hypothalamicus periventricularis anterior. Cajal described a connection from the septum to the principal and presumably the posterior or accessory nucleus of the tuber. This is comparable, but not entirely equivalent, to the medial forebrain connections described by Gurdjian for the posterior, lateral, ventromedial and dorsomedial hypothalamic nuclei. Coursing with the fornix-bundle for part of their path, in the rat at least, are fibers from the hippocampus and the amygdaloid region, termed medial corticohypothalamic and amygdalohypothalamic fibers. They supply fibers to the medial group of hypothalamic nuclei, external to the periventricular gray matter and to the posterior hypothalamic periventricular gray (Fig. 42 *a*). According to Cajal and others, the tangential nucleus receives fibers of Meynert's dorsal supra-optic decussation (Fig. 42 *j*). Gurdjian regarded his nucleus supra-opticus diffusus as possibly a bed-nucleus for Ganser's commissure; his dorsal premammillary nucleus is connected with its fellow of the opposite side and with the medial mammillary nucleus. Wallenberg (59), Cajal, Papez (41, 42) and Gurdjian (18) carried fibers of the mammillary peduncle forward to the tuber cinereum region. Papez believed that these fibers terminate in the lateral hypothalamic nucleus. They are likewise carried to the dorsal premammillary nucleus, in the diagram, where it is believed they also terminate. According to Gurdjian, the lateral, the posterior and the dorsomedial hypothalamic nuclei contribute fibers to the periventricular system, as do likewise the ventral premammillary and both dorsal and ventral divisions of the posterior periventricular nucleus. Cajal emphasized connections between the mammillary nucleus and the principal (ventromedial hypothalamic) nucleus. In

addition to these fibers, various connections are made with subthalamic centres. Moreover, impulses from the dorsal thalamus, either directly or by way of a synapse in ventral or subthalamic centres, undoubtedly reach these areas. According to various observers (Foix and Nicolesco (15) and others), ansa lenticularis fibers reach the tuber cinereum region. Part of such fibers at least appear to terminate directly in the periventricular gray matter. These connections may be summarized briefly as follows: the tuber cinereum region receives incoming impulses from the olfactosomatic correlation centres, the nucleus amygdalae, by way of the stria terminalis and the medial amygdalohypothalamic tract, from the olfactory cortex of the hemisphere by the medial corticohypothalamic tract and from the basal olfactory areas, including the parolfactory or septal nuclei, through the medial forebrain bundle. Nerve-impulses, of a character as yet not definitely known, reach the area from lower, and probably contralateral bulbar centres, by way of the mammillary peduncle. The discharge path appears to go in part indirectly by way of the subthalamic centres, but particularly through a periventricular system which connects the hypothalamic and pre-optic visceral regions with the midline areas of the dorsal thalamus, and particularly with the tectal and dorsal tegmental region and perhaps with areas further caudad. From the tectal areas by way of tectolbulbar and spinal paths and from the dorsal tegmental nucleus by way of the dorsal longitudinal fasciculus impulses pass to somatic efferent and particularly visceral efferent centres of the brain and spinal cord.

Dorsal Thalamus

The dorsal thalamus is divided into lateral and medial portions by the internal medullary lamina. To the medial division belong the anterior and medial nuclear groups and the nuclei of the midline. In the lateral portion are the lateral and ventral thalamic nuclei with their various subdivisions, the posterior nucleus, the pulvinar, the medial and lateral geniculate nuclei, the pretectal nucleus and certain smaller groups which will not be discussed here.

Anterior nuclei. The anterior portion is divided usually into three nuclei, which have received various designations and to which the authors are applying the names,—anterior dorsal, anterior ventral and anterior medial. These three nuclei lie in the dorsal cephalic portion

of the thalamus. In general, their relative position with reference to each other is indicated by their names, but this varies somewhat with different mammals. The anterior ventral and the anterior medial nuclei receive the mammillothalamic tract. According to Cajal, fibers from

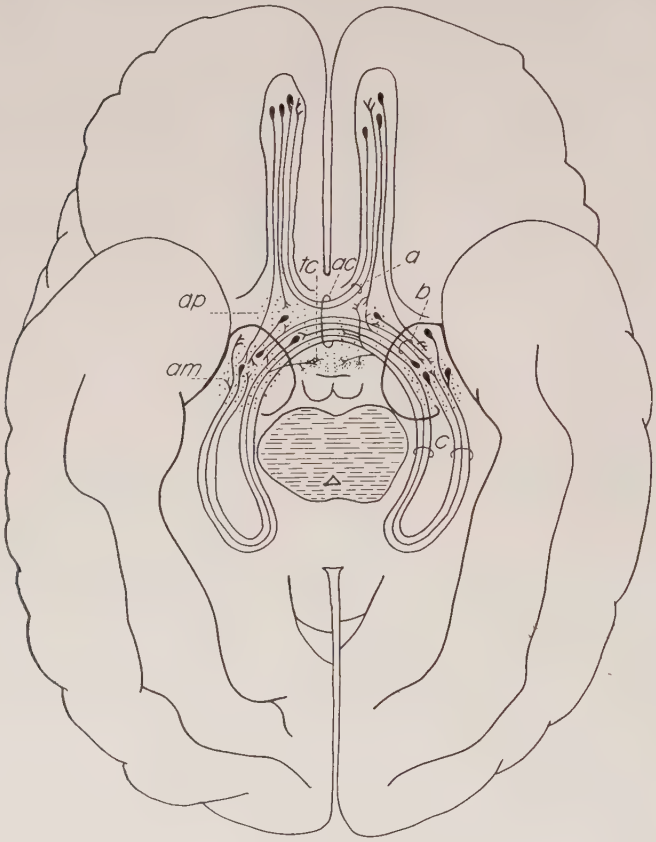

FIG. 43. Components of the anterior commissure: *a*, interbulbar component of the anterior commissure; *ac*, anterior commissure; *am*, amygdaloid nucleus; *ap*, anterior perforated space; *b*, intertemporal component of the anterior commissure; *c*, stria terminalis component of the anterior commissure; *tc*, tuber cinereum.

this bundle also reach the anterior dorsal nucleus. The anterior dorsal and the anterior ventral nuclei are connected with the cortex by way of the anterior thalamic radiations. The accounts of these fibers

in the literature suggest that the impulses may pass in both directions, although particular emphasis has been laid on the corticothalamic path (Déjerine (11)). Commissural fibers interconnect these nuclei with their fellows of the opposite side, and internuclear fibers associate them with each other and with the adjoining lateral and medial nuclei of the thalamus. Fibers from these anterior nuclei, and more particularly from the anterior ventral group, pass to the striatum, where they terminate in part in relation with the caudate nucleus. The connections of these groups with the cortex have been discussed by Cajal (9), d'Hollander (26), Ariëns Kappers (32), and Gurdjian (18). Cajal described the mammillothalamic tract in detail, and it has been generally recognized by students of the mammalian thalamus. Vogt (57), d'Hollander and Gurdjian laid particular stress on the commissural fibers; Ariëns Kappers and particularly von Monakow (38) emphasized the importance of the cortical connections.

The anterior dorsal, the most cephalic and the most dorsal of the group as its name implies, was described by Nissl (40), by Münzer and Wiener (39) and by d'Hollander for the rabbit, and by Gurdjian for the rat. Cajal (9) termed it *noyau angulaire* in the mouse, and Friedemann (17) and Vogt (57) described it for the monkey under the name of the anterior accessory thalamic nucleus. It is the nucleus anterior *b* of Winkler and Potter (64, 65), in the rabbit and the cat, and the anterior *c* of von Monakow (38). Von Kölliker (33) included it in the superior part of his intermediate nucleus, and Sachs (50) and Ingvar (30) applied to it the name of nuclei dorsales disseminati. Da Fano (10) included it under the nucleus zonalis, and it is a part of the nucleus reuniens of Malone (35). It has been given various other names by workers on the diencephalon.

The second nucleus of the anterior group is the so-called nucleus anterior ventralis. It has been described under this name by Münzer and Wiener (39) and d'Hollander for the rabbit, and by Gurdjian for the rat. It is the nucleus anterior *a* of von Monakow and Winkler and Potter, and the dorsal superior nucleus of Cajal. Vogt called it the principal anterior nucleus, and Friedemann the anterior nucleus. It, with the other two nuclear groups, was included by Kappers in his anterior nucleus. Nissl combined the anterior ventral and anterior medial nuclei under the term of anterior ventral nucleus, but split it into secondary divisions which do not correspond with those of other authors. Sachs combined the nucleus anterior ventralis with the nucleus anterior medialis and gave the name of nucleus dorsalis magnus to the group. A similar combination of nuclei was called nucleus commissuralis thalami pars dorsalis by Malone.

Nucleus anterior medialis, the third member of the group is the nucleus anterior *b* of von Monakow, probably the nucleus anterior *a* (Fig. 41) of Da Fano, the dorsal inferior nucleus of Cajal, the nucleus anterior of Friedemann, and the nucleus anterior *c* of Winkler and Potter; it is the nucleus anterior medialis of Münzer and Wiener, d'Hollander and Gurdjian, and the medialen Nebenkern *c* of Kappers.

Medial nuclei. The medial nuclei, as a group, lie ventral and later posterior to the anterior nuclei just described. They are medial to the lateral nucleus, and medial and dorsomedial to the ventral nucleus. They are more or less distinctly separated from the ventricular wall by the so-called nuclei of the midline. To this medial group belong several distinct cell-masses characterized by differences in cell-type and fiber-connections. Of these the most conspicuous to be considered is the nucleus medialis dorsalis, which occupies much of the medial portion of the thalamus, ventral and then caudal to the anterior group, lateral to the midline nuclei and medial to the internal medullary lamina. An inner large-celled part (Friedemann) can be differentiated from the remainder of the nucleus. Between it and the ventral medial nucleus in many forms is the lateral extension of the central nucleus, the paracentral nucleus. Vogt, Cajal and others established connections of this nucleus with the cortex; and it is connected also with the striatum. It is generally conceded that in lower mammals commissural fibers connect it with the homologous nucleus of the other side. According to Probst (43, 44), some lemnisci fibers appear to reach it. These are probably trigeminal fibers.

This nucleus is the medialis *a* of von Monakow and *b* of Winkler and Potter, the nucleus medialis of Sachs, the central gray nucleus of von Kölliker and the posterior medial nucleus of Nissl. By certain observers it has been divided secondarily into three parts. Thus, in the monkey, Friedemann described the chief medial nucleus with a zonal and a medial large-celled portion. These correspond to the divisions given by Kappers who termed the large-celled part the nucleus magnocellularis. Observers in general have recognized this group of nuclei.

Ventral to the chief medial nucleus is the nucleus submedius of Vogt and others, in part at least the nucleus medialis ventralis of certain workers. Associated with the more caudal part of the nucleus medialis dorsalis, or chief medial nucleus, is the nucleus parafascicularis (Cajal, Friedemann and others). The possible relations of this nucleus have been discussed under the account of the habenulopeduncular tract. It is said also to receive fibers from the internal capsule and to be connected with the tectum.

Another small nucleus to be reckoned with the medial gray matter is the nucleus parataenialis of d'Hollander, Gurdjian and others. This nucleus lies in general near the dorsomedial portion of the nucleus

medialis dorsalis in the forms in which it has been described and intervenes in part between the latter nucleus and the midline group with which the parataenial nucleus pars ependymarius of Friedemann is sometimes classified. It receives thalamic radiations from the internal capsule and in lower mammals is connected with the homologous nucleus of the other side by commissural fibers.

The nucleus parataenialis of d'Hollander, Gurdjian and others is the nucleus medialis parataenialis of Vogt, and probably part of the nucleus reuniens of Malone. Cajal termed it the lateral part of the superior nucleus of the raphe.

Nuclei of the midline. In lower mammals, such as rodents and carnivora, internal to the paired medial nuclei there is a series of cell-masses situated in the midline of the thalamus and for the most part unpaired. To this midline group the name of commissura media or nucleus reuniens has been frequently applied, but a detailed study of the area in rodents and carnivora, at least, and probably in many lower mammals, shows that the area is capable of subdivision into a number of distinct nuclear groups. In primates these midline nuclei have become relatively inconspicuous, and in fact as true median structures have disappeared in man. Yet traces of them remain in the periventricular regions of the dorsal thalamus of the human being.

These nuclei of the midline have two primary functions: they are concerned in interrelating the various nuclei of one side with their homologous nuclei of the other side by means of interstitial nuclei with associated commissural fibers. Such connections involve not only the main nuclei of the internal division but also the centromedian nucleus and the ventral nucleus. A second important consideration with regard to these nuclei is their interconnection with the tuber cinereum region by way of the periventricular system of fibers, and their discharge through this system to the tectal and tegmental areas of the midbrain, from which centres pathways are open to somatic and visceral efferent centres by way of tectospinal paths and the dorsal longitudinal fasciculus of Schultze. The portions of the nuclei of the midline which persist in the higher mammals are probably those parts concerned with periventricular and possibly internal capsule connections, while the portions which disappear are those that are more or less exclusively commissural. The periventricular gray matter, then, in dorsal as well as in ventral and subthalamic regions falls in part within the primitive discharge-path to the efferent centres.

It receives visceral impulses from the tuber cinereum region and correlates these with impulses received from somatic centres of the dorsal thalamus and with gustatory impulses. It connects with the dorsal medial nucleus of the thalamus and carries to that centre impulses from the visceral areas of the tuber cinereum. Internal capsule fibers have been traced to certain nuclei of the area but the direction of conduction is as yet unknown.

The following is a brief summary of certain of the more important midline groups found in subprimate forms: Beginning at the dorsal side of the diencephalon at a level passing through the cephalic part of the anterior nuclei, a nuclear mass is found in the midline which extends caudad throughout practically the whole extent of the diencephalon. This is the nucleus parataenialis, pars subependymarius of Friedemann, a part of the nuclei of the midline of Münzer and Wiener (39), and Nissl (40), and the nucleus paramedianus of Malone (35). It includes the paraependymal nucleus described for the cat by Winkler and Potter (65). It is the dorsal part of the nucleus reuniens of d'Hollander and the nucleus paraventricularis anterior and posterior of Gurdjian (18). In a plane passing through the anterior end of the medial habenular nucleus in the rat, Gurdjian found the commissural nuclei connecting the anterior dorsal and anterior medial thalamic nucleus. These lie just ventral to the nucleus paraventricularis anterior. Ventral to these commissural nuclei is the nucleus rhomboidalis, and below that the nucleus reuniens; further caudad the paired paraventricularis posterior replaces the anterior paraventricular group; the nucleus centralis occupies the former position of the nucleus rhomboidalis. After the disappearance of the nucleus reuniens, the nucleus commissuralis interventralis makes its appearance. The majority of these nuclear groups have been described in other mammalian forms. Thus the nucleus rhomboidalis of Gurdjian is a part of the middle portion of the nucleus reuniens of d'Hollander (26), a part of the nucleus of the midline of Münzer and Wiener, and is included in the commissura media of Sachs (50). According to Cajal (9), this nucleus receives corticothalamic and thalamocortical fibers. The nucleus reuniens of Gurdjian is the ventral arcuate nucleus of Münzer and Wiener, is a part of the nucleus reuniens of d'Hollander, and receives periventricular and inferior thalamic radiations. Commissural nuclei between the various thalamic centres have been described by d'Hollander and Cajal.

Centromedian nucleus. In its position and general relations in certain mammals, the centromedian nucleus appears to belong to the medial group; in its fiber connections and consequent functional significance, at least in higher mammals, it is more directly related to the ventral group of thalamic nuclei. Its inclusion in the latter group permits of certain generalizations which are of value in the present discussion, and consequently for convenience the authors have considered it with the divisions of the ventral nucleus. It is of signifi-

cance that differences in the statements regarding the functions of the medial nucleus can frequently be reconciled when the inclusion or exclusion of this nucleus within the medial division is taken into account. Sachs and others have regarded this nucleus as related particularly to the lateral division of the thalamus. Many comparative neurologists, as von Monokow (*med. b*), Winkler and Potter have placed it with the medial group. Frequently there has been an unfortunate confusion of this nucleus with the cells in the internal medullary lamina. Vogt, Friedemann and others have identified a centromedian nucleus. This nucleus receives thalamic radiations from the internal capsule, the impulses apparently passing in both directions. According to some, it receives the medial part of the medial lemniscus; and Foix and Nicolesco believe that it receives secondary ascending fibers from trigeminal centres, that is, trigeminal lemniscus.

Ventral nucleus. In lower mammals the ventral nucleus consists of a round or oval mass of cells, resembling the nucleus rotundus of reptiles and birds, with which, in agreement with Ingvar and others, the authors believe it should be homologized. This oval mass is secondarily differentiable into two portions in the rabbit (d'Hollander) and in the rat (Gurdjian). In carnivora the nucleus ventralis has lost its rotund form and can be divided into at least three distinct nuclear masses (Winkler and Potter (65)). In the monkey, Friedemann divided the area into caudal, medial and oral parts. A portion of his caudal and all of his medial division are comparable to the *noyau sensitif* of Cajal. This medial division alone is probably the semilunar nucleus of Déjerine, the arcuate nucleus of von Kölliker and is within ventralis *b* of von Monakow. The oral portion of the nucleus is probably the same as the anterior semilunar nucleus of Cajal. In higher mammals the ventral nucleus occupies a considerable portion of the thalamus. It is situated between the lateral and centromedial nuclei, on the one hand, and the zona incerta, on the other. Cephalad to the level of the centromedial nucleus it lies in relation with the medial nucleus. Anteriorly it is bordered on its lateral side by the reticular zone, but farther caudad it lies ventrolaterally in relation with the zona incerta. It is to be regarded as one of the most important nuclei of the thalamus, for here terminate the major portion of the great ascending sensory systems, and from the nucleus arise the great majority of the projection fibers to the postcentral areas of the cerebral cortex.

Because of their great significance with reference to the function of the thalamus, these secondary ascending pathways have been diagrammed to show their relations and relative position; the following account should be read in connection with the diagram:

Painful impulses from the body pass to the spinal ganglia by way of unmedullated components of the peripheral nerves. The cells of origin of the fibers lie in the dorsal root ganglia, and their neuraxes, which are likewise unmedullated or only faintly medullated, enter the cord, reach a position at the tip of the dorsal horn and become components of Lissauer's tract. Individual neuraxes bifurcate and ascend and descend for not more than two segments. They terminate around cells of the substantia gelatinosa of Rolando. For the details of this termination and for an account of these fibers in general the work of Ranson (47–49) should be consulted. The neuraxes of cells in the dorsal horn region of the cord carry these impulses across the midline to the ventrolateral part of the cord where, with others of their kind, they form the lateral spinothalamic tract. This tract occupies relatively a superficial position in its course through the cord, and retains this lateral position throughout much of its path. In the upper part of the pons region the lateral migration of the medial lemniscus brings the lateral spinothalamic path into close relation with the other lemnisci systems, and it runs forward as the most lateral component of the medial lemniscus to the more lateral parts of the ventral nucleus of the thalamus and to the centromedian nucleus of Luys. The main lateral spinothalamic tract is accompanied throughout its course by short fibers, contralateral and homolateral in type, which form a chain of neurones for the conveyance of the impulses to higher centres.

Tactile impulses are brought to the central nervous system over heavily medullated dendrites, the cells of origin of which are within the spinal ganglia. The neuraxes of such cells enter the cord with the medial division of the spinal nerves and bifurcate into long ascending and short descending branches. These branches give off collaterals at all levels of the cord through which they pass and these collaterals terminate in relation to dorsal horn gray matter. From this gray matter neuraxes of neurones of the second order, decussate in the anterior white commissure of the cord and run forward toward the higher centres as the ventral spinothalamic tract. In many cases the long ascending neuraxis of the primary neurone passes out of the cord to the nucleus gracilis or more frequently to the nucleus cuneatus of the medulla. The ventral spinothalamic tract has a ventral position throughout its course in the cord. Its position in the medulla is still a matter of dispute. According to Déjerine, whose results are shown in the accompanying diagram, the ventral spinothalamic tract comes into relation with the medial lemniscus within the medulla and runs forward with this fiber bundle. In the midbrain region, the ventral spinothalamic path lies medial to the lateral spinothalamic tract as the two become incorporated within the general lemniscus system (Fig. 44.

Proprioceptive impulses are brought forward from the body by way of the ascending fibers of the fasciculus gracilis and cuneatus. These fibers enter into synapse in the medullar nuclei of the fasciculi and then secondary neurones carry the

impulse by way of internal arcuates and the sensory decussation to the medial lemniscus of the opposite side. The work of Allen (1) indicates that secondary visceral fibers from the gustatory centres, and the cephalic half of the general visceral centres of the medulla likewise cross the midline and run forward with these proprioceptive fibers as components of the medial lemniscus. From the spinal and chief sensory nuclei of the trigeminus, secondary fibers cross the midline and take up a position adjacent to the other lemnisci bundles. These fibers from the trigeminal centres are termed the ventral secondary ascending trigeminal tract and carry probably impulses of pain, temperature and general tactile sensibility. Another path forward from the chief sensory nucleus of the trigeminal nerve, phylogenetically younger and probably forming the pathway where tactile discrimination is involved, is the dorsal secondary ascending path of the trigeminal nerve, which retains its more dorsal position and runs for most of its course independently of the lemnisci bundles. From the preceding account and by consultation of Figure 44, it is evident that the great ascending systems to the thalamus converge as they approach that area to form a great bundle of ascending fibers. Yet it is believed that they retain in the bundle their original position so that from outside toward the midline, the paths are successively lateral spinothalamic, ventral spinothalamic (ventral secondary trigeminal in close association) fibers and then gustatory and proprioceptive fibers from the medial lemniscus proper, with the dorsal secondary trigeminal tract lying outside the main mass. In their distribution within the thalamus, the evidence suggests that the more medial portions of the bundle reach the more medial parts of the ventral nucleus while the more lateral parts distribute to more lateral regions of this nuclear mass (Wallenberg (60)). It is known from the work of Vogt (57, 58) that the more medial part of the lemniscus reaches the medial and lateral caudal regions of the ventral nucleus of the thalamus, and that the trigeminal fibers and fibers from the dentate nucleus of the cerebellum and the red nucleus reach the intermediate lateral portions of the ventral nucleus. Into the lateral parts of the nucleus pass likewise the spinothalamic tracts. The dentothalamic and rubrothalamic fibers bring forward by way of the cerebellum proprioceptive impulses including those from the vestibular complex. The lateral spinothalamic and the trigeminal components pass likewise to the centromedian nucleus, and fibers of the median lemniscus of character as yet unknown reach the posterior nucleus of the thalamus. Medial lemnisci fibers are also distributed to the posterior nucleus and according to Probst (43, 44), to some extent, to the medial nucleus. Von Monakow regarded the lateral nucleus as the thalamic centre connected with the lower limb centres of the precentral and postcentral gyri. This would imply lemnisci connections with the lateral nucleus. Flechsig (14) carried projection fibers from the anterior and posterior parts of the ventrolateral nuclei (ventral nucleus region) to the lower third and upper third of the postcentral convolutions (the posterior to upper third of central). The middle third of the central convolutions received fibers from the region of the arcuate and centromedian nuclei.

This account indicates that general sensibility, tactile, temperature and pain impulses, from the head and body, are brought to the ventral

nucleus of the thalamus by way of the ventral ascending trigeminal tract and the lateral and ventral spinothalamic systems. Of these, the trigeminal components are known to reach lateral intermediate parts of the thalamus, and the spinothalamic components are believed to reach its lateral portion. Proprioceptive impulses from vestibular and other bulbar and spinal centres are distributed by way of the superior cerebellar peduncles to the areas reached by the secondary trigeminal fibers. Proprioceptive impulses, exteroceptive for tactile discrimination (and probably gustatory fibers) also reach the ventral nucleus of the thalamus. Thus, this nucleus is, above all, the thalamic centre of termination for exteroceptive, proprioceptive and possibly gustatory impulses. Here they are relayed to motor centres of the ventral thalamus by way of connections with the zona incerta and possibly other ventral nuclei, and thus make provision for thalamic reflexes. The ventral nucleus of the thalamus is connected with the striatal areas by thalamostriatal fibers, particularly by inferior thalamic radiations (ansa peduncularis), and it also has connections with the other thalamic nuclei by way of internuclear fibers and so provides for interthalamic correlation. It sends fibers through the posterior limb of the internal capsule for the projection of the various sensory impulses on the cerebral cortex.

Lateral nucleus. The differentiation of the lateral nucleus is in direct relation to the position of the animal in the mammalian scale of development. Thus, in the lower mammals it is a single nuclear mass with possibly a slightly differentiated external posterior portion, which receives optic fibers, has connections with the lateral geniculate and so is looking forward to the development of the pulvinar. In the cat, Winkler and Potter (65) have demonstrated the presence of two lateral nuclei (nuclei lateralis *a* and *b*) which are here termed nucleus lateralis anterior and nucleus lateralis posterior. Vogt (57) described three and Friedemann (17) three (two major and a minor) nuclear masses with subdivisions in the lateral nucleus of the monkey, and von Monakow (38) identified an anterodorsal and a caudoventral portion in the lateral thalamic nucleus in man.

The nucleus lateralis is interconnected with the ventral and medial nuclei of the thalamus. Various observers have traced fibers of the internal capsule to it, but there is uncertainty in regard to the direction of the impulse. Von Monakow regarded this nucleus as connected with frontal, precentral, postcentral and parietal areas. In the authors'

judgment both ventral and lateral nuclei of the thalamus increase in size and nuclear differentiation with the development and differentiation of the cortical centres. The ventral nucleus differentiates with the projection centres, the presence within it of specific nuclei forecasting and postulating the appearance of the localization within these cortical areas, while the lateral nucleus develops along with the non-projection or essentially association cortical areas, perhaps also with the projection cortex.

Along the border of the lateral and ventral nuclei of the thalamus, intercalated in the course of internal capsule fibers, are found scattered masses of gray matter which constitute the reticular nuclei.

Pulvinar. The pulvinar is present as a distinct nuclear group only in higher mammals. It has been described for the cat (Winkler and Potter, (65)), and for the monkey (Friedemann (17) and Vogt (57)). The latter observers have indicated the presence of many subdivisions within this nuclear mass, but since such subdivisions are based on the cyto-architectonic and myelo-architectonic structure of the nucleus rather than on specific fiber connections, they will not be discussed further here. Most observers are agreed that the pulvinar receives direct optic fibers and that it is connected with the lateral geniculate nucleus and with the superior colliculus. Connections between the pulvinar and the area striata of the cortex have been described repeatedly, but there appears still to be some question with regard to the direction of the conduction of impulses.

Lateral geniculate body. The lateral geniculate body exhibits two nuclei, a dorsal and a ventral, in mammals through the lower primates (Woollard (66) and others). A distinct ventral nucleus has not been demonstrated in higher primates, including man. Of these two nuclei, the ventral is phylogenetically the older. As far down as fishes, collaterals of the optic tract terminate in the diencephalon, and in amphibians an optic thalamic nucleus is present. This becomes more highly differentiated in reptiles and is the anlage of the ventral nucleus of the lateral geniculate body of higher forms. In all submammalian types the lateral geniculate body is pre-eminently a dependency of the tectum, with which it is connected by numerous tracts conducting impulses in both directions. Passing caudad from the lateral geniculate body in Varanus (Beccari (2)), and in the alligator (Huber and Crosby (27)), is a descending tract to the motor centres, the fasciculus geniculatus descendens. The presence of numerous

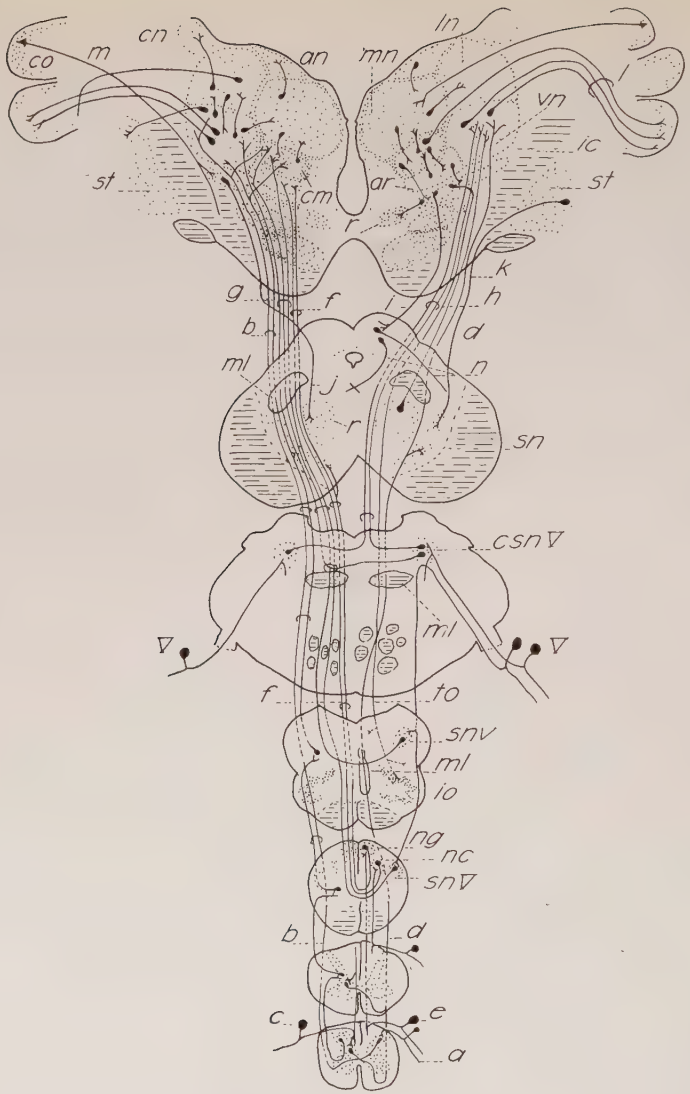

FIG. 44. Diagram illustrating the relations of the lemnisci system: *a*, neurone carrying sense of pain or temperature; *an*, anterior thalamic nucleus; *ar*, arcuate nucleus; *b*, lateral spinothalamic tract; *c*, neurone carrying tactile impulses; *cm*, centromedian nucleus of Luys; *cn*, caudate nucleus; *co*, cortex; *csnV*, chief sensory nucleus of the fifth nerve; *d*, ventral spinothalamic tract; *e*, proprioceptive neurone; *f*, proprioceptive portion of medial lemniscus; *g*, ventral trigeminal projection tract; *h*, dorsal trigeminal projection tract; *i*, incertotectal tract; *ic*, internal capsule; *io*, inferior olivary nucleus; *j*, incertorubral tract; *k*, strionigral tract; *l*, thalamo-cortical tract to postcentral gyrus; *ln*, lateral thalamic nucleus; *m*, corticospinal tract from precentral gyrus; *ml*, medial lemniscus; *mn*, medial thalamic nucleus; *n*, crossed and uncrossed tectospinal tracts; *nc*, nucleus cuneatus; *ng*, nucleus gracilis; *r*, red nucleus; *sn*, substantia nigra; *snV*, spinal nucleus of the fifth nerve; *st*, striatum; *to*, thalamo-olivary tract; *vn*, ventral thalamic nucleus.

tectogeniculate fibers and of this descending tract indicates that one important function of the primitive geniculate body is to provide a mechanism for the correlation of optic impulses with those from tectal centres (which include in these forms auditory, tactile and general sensibility as well as optic), and provision of a means of discharge to motor centres. In Sphenedon (Cairney (8)) there is the beginning of a dorsal nucleus of the lateral geniculate body. Even in lower mammals the latter nucleus has shown relative increase, while the ventral nucleus, with a decrease in the dominance of the tectum in mammalian forms, is relatively smaller and shows relatively less differentiation. The relations in such a mammalian form are indicated in the subdiagram of Figure 45. Here, incoming optic fibers are distributed to the primitive pulvinar and to the ventral and dorsal nuclei of the lateral geniculate body, the dorsal nucleus being connected chiefly with the cerebral cortex while the ventral nucleus is interconnected with the tectum and gives rise to the descending fasciculus. Woollard has shown, in the study of a series of closely related higher mammals including primates, that there exists a progressive disappearance of that part of the lateral geniculate body which is related to the tectal centres. As previously stated, this nucleus has not been demonstrated in man. The dorsal part of the lateral geniculate nucleus has increased progressively in the mammalian phylum, so that in higher mammals, such as the carnivora, it has acquired an elaborate laminated structure, the cyto-architecture of which has been described by several recent observers (Minkowski (36, 37) and others), and recently has been modeled and described in detail by Thuma (54) for the cat. For further details, reference should be made to the original contributions. Similarly, the details of the projection of the quadrants of the retina on the lateral geniculate nucleus and the details of its projection on the cortical area must be obtained from the literature. There have been so many recent reviews of the literature dealing with this subject that further discussion here is deemed unnecessary. Reference is here made to the work of Minkowski (36, 37), Brouwer (5, 6), Brouwer and Zeeman (7), Henschen (20), Putnam (46). From the foregoing statements it will be seen that the lateral geniculate body receives optic fibers, that it is interconnected with the tectum and with the pulvinar, and that it sends fibers to the area striata of the cortex. Whether or not a descending geniculate fasciculus is present in higher mammals, is uncertain.

Optic tract (Fig. 45). From the rod-and-cone layer of the retina, nerve-impulses are passed to the bipolar cells and from there to the ganglion-cells of the retinal layer. The neuraxes of these ganglion-cells course to the brain as the optic nerve, those fibers from the nasal side of the retina decussating in the optic chiasm and those from the temporal portion passing back on the same side. Beyond the chiasm these crossed and uncrossed fibers form the optic tract which distributes to the superior colliculus, to the lateral geniculate and to the pulvinar; the fibers (mainly crossed) to the superior colliculus are concerned with light reflexes and the impulse, after a synapse in this region, is distributed either by the radiations of Meynert to the Edinger-Westphal nucleus of the third segment, or by the tecto-spinal path and presumably the medial one to the intermediolateral column in the first four segments, of the thoracic cord. From the Edinger-Westphal nucleus, impulses are carried over the oculomotor nerve to the ciliary ganglion, where these preganglionic fibers enter into synapse with the cell-bodies of postganglionic neurones which are distributed to the ciliary muscle and to the circular fibers of the iris. They provide thus for accommodation and are the sphincter fibers of the pupil. The preganglionic fibers from the thoracic cord leave by way of the spinal nerves, pass out to the chain-ganglia and forward along the sympathetic chain to the superior cervical sympathetic ganglion where they form a synapse. Postganglionic fibers run forward from this ganglion to the dilator apparatus of the eye and so permit an increase in the size of the pupil. The optic fibers which terminated in the lateral geniculate body are in synaptic connection with neurones, the neuraxes of which pass to the superior colliculus, to the pulvinar or to the area striata of the cerebral cortex. Those to the tectum run in the peduncle of the superior colliculus. This peduncle carries also fibers from the pulvinar and from the lateral geniculate and for part of their course fibers directly from the area striata of the cerebral cortex to the superior colliculus. Corticothalamic fibers likewise pass to the pulvinar. There is disagreement as to the presence of thalamocortical fibers from this nucleus to the cerebral cortex. Visual reflexes are mediated by way of the thalamus, at least in the highest mammals, and disappear with the destruction of the optic thalamic centres even if the superior colliculus and the tracts passing to and from it are intact. An efferent pathway, however, for visual reflexes may pass from the thalamus to the superior colliculus and then by way of the radiations of Meynert to the nuclei of the extrinsic muscles of the eye in the oculomotor, trochlear and abducens nerves, the latter two nuclei being connected with the nuclei of the oculomotor nerve by means of the medial longitudinal fasciculus.

In addition to the optic tract fibers thus far described, there are the two accessory optic tracts of Bochenek (4). The optic fibers in the anterior accessory tract, after a partial decussation in the optic chiasm, separate from the main optic bundles and run caudad in the depths of the thalamus to the subthalamic nucleus of Luys. The posterior accessory optic tract of Bochenek is better known as the tractus pedunculus transversus. This tract runs caudad along the ventral surface in relation to the cerebral peduncle and then turns dorsad to terminate in the nucleus of the tract, which is situated along the side of the peduncle at about the level of the interpeduncular nucleus and slightly dorsolateral to it. The nucleus of the tractus pedunculus transversus has a connection with the oculomotor nucleus. This account should be studied with Figure 45 in mind.

The medial geniculate body has been divided into several nuclear groups, but homologies in the different forms are difficult to make by reason of the absence of details of fiber connections in many cases. Cajal divided the nuclear mass into a superior lobe, associated with Gudden's commissure and the peduncle of the inferior colliculus, and an inferior lobe, which received fibers of the lateral lemniscus. Both lobes gave rise to thalamocortical fibers. Associated with these nuclear masses was recognized an internal nucleus, consisting of large cells, which was in association with the nucleus of the lateral lemniscus. Three portions of the medial geniculate nucleus were figured by Winkler and Potter (65) in their atlas on the cat. The diagram presented in Figure 46 represents the authors' conception of the auditory connections.

Auditory connections (Fig. 46). The neurones of the first order for auditory impulses lie in the spiral, cochlear ganglion. Their neuraxes enter the medulla and form a synapse in the dorsal and ventral cochlear nuclei. From the dorsal cochlear nucleus fibers pass as stria medullaris acoustici across the floor of the fourth ventricle to the midline, where they swing ventrolaterad to enter the lateral lemniscus of the same and opposite sides. From the cells of the ventral cochlear nucleus, neuraxes course mediad, cross the midline and enter the lateral lemniscus of the opposite side; on their way they give collateral and stem-fibers to the superior olivary nuclei and the trapezoid nuclei of the two sides. These fibers, which constitute the trapezoid body, are joined by tertiary fibers from the trapezoid nuclei. Thus at about the middle of the pons, the lateral lemniscus is composed of crossed and uncrossed fibers arising from the neurones of the dorsal cochlear nucleus and the trapezoid nucleus, and fibers from the contralateral ventral cochlear nucleus. As the lateral lemniscus runs cephalad, certain of its fibers come into synaptic relation with scattered gray matter termed the nucleus of the lateral lemniscus. The lateral lemniscus terminates in the inferior colliculus of the midbrain, and the medial geniculate nucleus of the thalamus. From the inferior colliculus impulses are likewise carried to the medial geniculate by way of its peduncle. Acoustico-optic or intertectal fibers connect the inferior with the superior colliculus and thus make possible the transmission of auditory impulses from inferior to superior regions and then to motor centres of the bulb and cord by way of tectobulbar and tectospinal paths. The peduncle of the superior olive, which connects with the motor nucleus of the sixth nerve, relays auditory impulses to this nucleus, whence they are distributed by way of the medial longitudinal fasciculus to the motor nuclei of the third and fourth nerves and to the spinal motor nucleus of the eleventh cranial nerve. Thus provision is made for the reflex of turning the head and eyes in the direction of the sound. The auditory impulses reaching the medial geniculate by way of the lateral lemniscus and the peduncle of the medial geniculate, after relay in this thalamic centre, are carried to the cortex by way of sublenticular auditory radiations to Heschl's convolution. The various paths here described are to be seen in Figure 46.

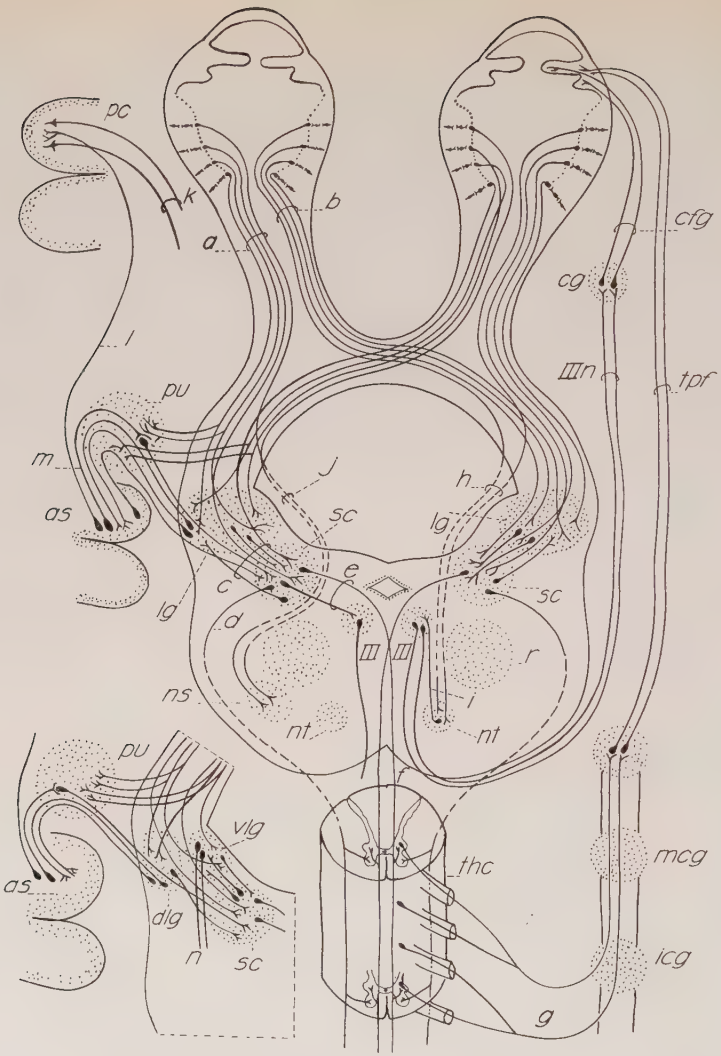

FIG. 45. Optic connections: *a*, uncrossed or temporal optic fibers; *as*, area striata; *b*, crossed or nasal optic fibers; *c*, brachium or peduncle of the superior colliculus; *cg*, ciliary ganglion; *cfg*, craniosacral postganglionic fibers; *d*, lateral tectospinal path; *e*, Meynert's radiation; *f*, medial tectospinal path; *g*, thoracico-lumbar preganglionic fibers; *h*, tractus pedunculus transversus (posterior accessory optic tract of Bochenek); *i*, connections between the nucleus of the tractus pedunculus transversus and the nucleus of the third nerve; *icg*, inferior cervical sympathetic ganglion; *j*, anterior accessory optic tract of Bochenek; *k*, corticospinal tract; *l*, cortical association path; *lg*, lateral geniculate; *m*, corticopulvinar fibers; *mcg*, middle cervical sympathetic ganglion; *n*, fasciculus geniculatus descendens of Beccari; *ns*, nucleus subthalamicus; *nt*, nucleus of the tractus pedunculus transversus; *pc*, precentral cortex; *pu*, pulvinar; *r*, red nucleus; *sc*, superior colliculus; *scg*, superior cervical sympathetic ganglion; *thc*, thoracic spinal cord; *tpf*, thoracico-lumbar postganglionic fibers; *vlg*, ventral nucleus of the lateral geniculate; *III*, efferent nucleus of the third nerve; *IIIn*, third nerve.

A posterior thalamic nucleus has been described in various mammals, but the area so designated has not always received the same delimitation. Thus, the posterior nucleus of one author may include the pretectal nucleus, or part of the lateral nucleus, or even the pregeniculate nucleus of another author. Since various mammalian forms have been considered and in most instances the fiber connections are unknown, it is extremely difficult and on the whole, unprofitable to attempt to make exact homologies at the present time. In mammals, the posterior thalamic nucleus lies at the caudal end of the diencephalon, extending back to the midbrain region. On the whole, its position is ventral and ventromedial to the lateral nucleus, and for the most part dorsomedial to the lateral geniculate body. It receives fibers from the medial lemniscus and is connected with the tectum and the cortex.

In submammalian forms there is a well developed group of nuclei in the boundary region between diencephalon and tectum. With the reduction of the superior collicular portion of the tectum this pretectal gray matter is apparently reduced. In only a few forms, such as the rat (Gurdjian (18)), has a definite pretectal nucleus been described; usually the area has been included under the posterior thalamic nucleus (d'Hollander (26)). To what extent other portions of the posterior nucleus are to be regarded as derivatives of the primitive pretectal group is at present uncertain. When differentiable, this pretectal nucleus is connected with the tectum. It is the authors' conviction that there is a distinct need of a more thorough understanding of tectothalamic and thalamotectal connections in mammals, particularly in view of their phylogenetic significance.

Ventral Thalamus

The ventral thalamus, or the subthalamus, one of the major divisions of the diencephalon, in general lying ventral to the sulcus medius, is to be regarded particularly as a place of origin or synapse of efferent pathways. To this region are allocated the zona incerta, fields H of Forel (16), the entopeduncular nucleus, the nucleus subthalamicus and the cephalic prolongations of the substantia nigra and the nucleus ruber. In addition to these, there are smaller nuclear groups of which no discussion will be attempted here.

Zona incerta. The zona incerta consists of scattered cells lying in the course of certain efferent fiber-bundles from the internal capsule.

It is situated in the dorsal part of the subthalamus, immediately ventral to the ventral thalamic nucleus, and is not sharply delimited from the surrounding area. This area probably receives collaterals from corticospinal and corticobulbar fibers, possibly also terminal fibers from the cortex. It is connected with the striatum through collaterals of fibers found in the ansa lenticularis; it is connected with the medial and ventral nuclei of the dorsal thalamus and probably with the contralateral homologous area through the fibers of Meynert's commissure (Fig. 40). This nucleus probably contributes fibers to the descending motor pathways, and is connected with the tectum and tegmentum of the midbrain by way of incertotectal and incertotegmental paths. It is connected with the rostral end of the red nucleus and the subthalamic nucleus, and probably with other nuclei of the ventral thalamus. It probably gives rise to thalamobulbar and thalamo-olivary paths (in part), but there is need of confirmation for these last two connections. These connections for the zona incerta and the remainder of ventral thalamus or subthalamus are based on personal observation and the accounts of other authors, among whom may be mentioned von Monakow (38), Déjerine (11), Cajal (9), Wilson (63), Hunt (29), Tilney and Riley (53), Foix and Nicolesco (15) and others.[2] Fields H_1 and H_2 of Forel (16) consist of scattered gray fibers in the course of distinct bundles (portions of the efferent systems from the corpus striatum) which were described by this author and are known as the radiations of Forel. Of these radiations H_1 is the thalamic fasciculus and H_2 the lenticular fasciculus of Forel.

Entopeduncular nucleus. The term entopeduncular nucleus is applied to a small group of relatively large cells found in conjunction with the ansa lenticularis; it constitutes a region of synapse for efferent pathways.

Subthalamic nucleus. The subthalamic nucleus, or hypothalamic nucleus or the corpus Luysi, an approximately oval nuclear mass in higher mammals, is situated in close relation to the rostral end of the

[2] In Figure 47, are shown bundles passing directly from the caudate nucleus and the putamen, as well as from the globus pallidus, into the ventral division of the ansa lenticularis; this follows the recent account of Foix and Nicolesco (15). It is not entirely in agreement with the statement of Wilson (63), based on the monkey, that the main striofugal and striopetal paths come into relation only with the globus pallidus and are not directly related with the putamen and globus pallidus.

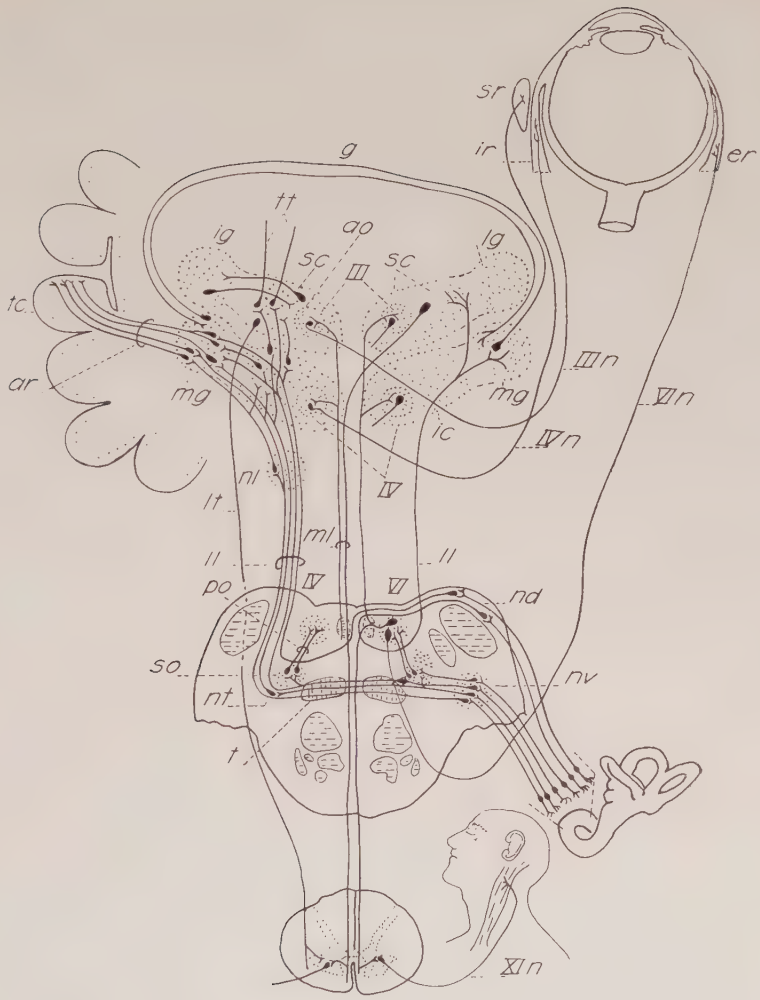

FIG. 46. Auditory connections: *ao*, acoustico-optic radiations; *ar*, auditory radiations; *er*, external rectus; *g*, Gudden's commissure; *ic*, inferior colliculus; *ir*, internal rectus; *lg*, lateral geniculate body; *lt*, lateral tectospinal path; *ll*, lateral lemniscus; *mg*, medial geniculate; *ml*, median longitudinal fasciculus; *nd*, dorsal cochlear nucleus; *nl*, nucleus of the lateral lemniscus; *nt*, nucleus of the trapezoid body; *nv*, ventral cochlear nucleus; *po*, superior olivary peduncle; *so*, superior olivary nucleus; *sc*, superior colliculus; *sr*, superior rectus; *t*, trapezoid body; *tc*, temporal cortex; *tt*, tectothalamic tract; *III*, nucleus of the third nerve; *IIIn*, oculomotor nerve; *IV*, nucleus of the fourth nerve; *IVn*, trochlear nerve; *VI*, nucleus of the sixth nerve; *VIn*, abducens nerve; *XIn*, spinal accessory nerve.

substantia nigra. It is connected with its fellow of the opposite side through commissural fibers found in the supramammillary commissure (Fig. 47) and with the substantia nigra and the zona incerta. It is connected with the striatum (caudate nucleus and putamen and globus pallidus) by way of the striosubthalamic fasciculus. The subthalamic nucleus receives also the posterior accessory optic tract of Bochenek (4).

Substantia nigra. The substantia nigra, constituting a mass of gray matter lying in definite relation to the cerebral peduncle and extending forward from the midbrain region into the ventral thalamus, is composed of cells having a definite pigmentation, which apparently increases definitely with the advent of puberty. This nuclear mass, in addition to other internuclear connections with subthalamic nuclear masses, is connected with the globus pallidus by way of the medial and ventral divisions of the ansa lenticularis of von Monakow (38), and is believed to receive collaterals from corticobulbar and corticospinal fibers and also has tectal and tegmental connections.

Nucleus ruber. The nucleus ruber consists of a small- and a large-celled nuclear portion, as has been indicated by the work of von Monakow and others; and as has also been confirmed by the authors' own material. The general appearance, the position and relations of this nucleus are so generally known that a detailed description may with propriety be omitted at this time. Afferent impulses reach this nucleus from the cerebral cortex by way of the corticorubral path, from the striatum by way of the dorsal and ventral divisions of the ansa lenticularis of von Monakow, from the zona incerta and probably other subthalamic centres by way of incertorubral and other internulcear connections, and from the dentate nucleus of the cerebellum through crossed fibers of the superior cerebellar peduncles. The main efferent pathways are the rubrothalamic, the rubroreticular or rubrobulbar and rubrospinal of von Monakow. The rubrothalamic, with the secondary ascending trigeminal fibers, form the fasciculus prelemniscalis of Vogt, which, according to this author, distributes to the caudal portion of the ventral nucleus of the dorsal thalamus (Va_1 of Vogt (57, 58), and of Friedemann (17)). The rubrobulbar and rubrospinal paths pass to motor centres of the bulb and spinal cord. The main afferent and efferent pathways, as they relate to the subthalamus, are delimited primarily in Figure 47. Other figures of the series, particularly Figure 44, show certain further

connections. Attention is called especially to the connections of the dorsal, medial, and ventral portions of the ansa lenticularis of von Monakow.

COMMENT ON THE DORSAL AND VENTRAL THALAMUS

The general functions of the dorsal and ventral thalamus have been suggested in the introductory lines followed by a discussion of the nuclear pattern in its relation to fiber connections. An attempt may now be made to state, at least in general terms, the relations existing between structure and function.

The medial division of the thalamus has been shown to consist of an anterior, medial and midline group of nuclei. The anterior group receives olfactovisceral impulses from the hypothalamus; the medial group receives tactile, pain and temperature impulses, but for the most part indirectly by way of internuclear fibers from the ventral thalamic nucleus. Olfactovisceral impulses, by way of the periventricular system from the tuber cinereum, reach certain nuclei of the midline and so directly or indirectly the medial nucleus. The interrelation of this nucleus with the anterior nucleus brings to it also olfactovisceral impulses. Thus the medial nucleus becomes a centre of correlation for exteroceptive impulses (general sensibility, pain and temperature) and interoceptive impulses (olfactory, gustatory and possibly general visceral sensations); but to what extent proprioceptive impulses reach it, is uncertain. Within themselves the medial nucleus and its associated nuclei present no pattern, nor do they have the specific type of connections, which would suggest a definite localization of impulses within them; on the contrary, they indicate such interrelation and correlation of impulses as would provide the anatomic basis for general affective tone. A further confirmation of the lack of localization within the medial nucleus and the medial division in general, is to be found in the fact that it connects with the frontal lobe, regarded as an association rather than as a projection centre. Tilney and Riley (53) regard the latter connection as providing the anatomic basis for personality and behavior. It is certain that impulses reaching this area from the medial nucleus will frequently represent the integration of a variety of bodily stimuli, and that such impulses discharging through association fibers to afferent and particularly to efferent centres will modify to a considerable degree the type of response to a given stimulation. However, just as the stimuli of the medial division

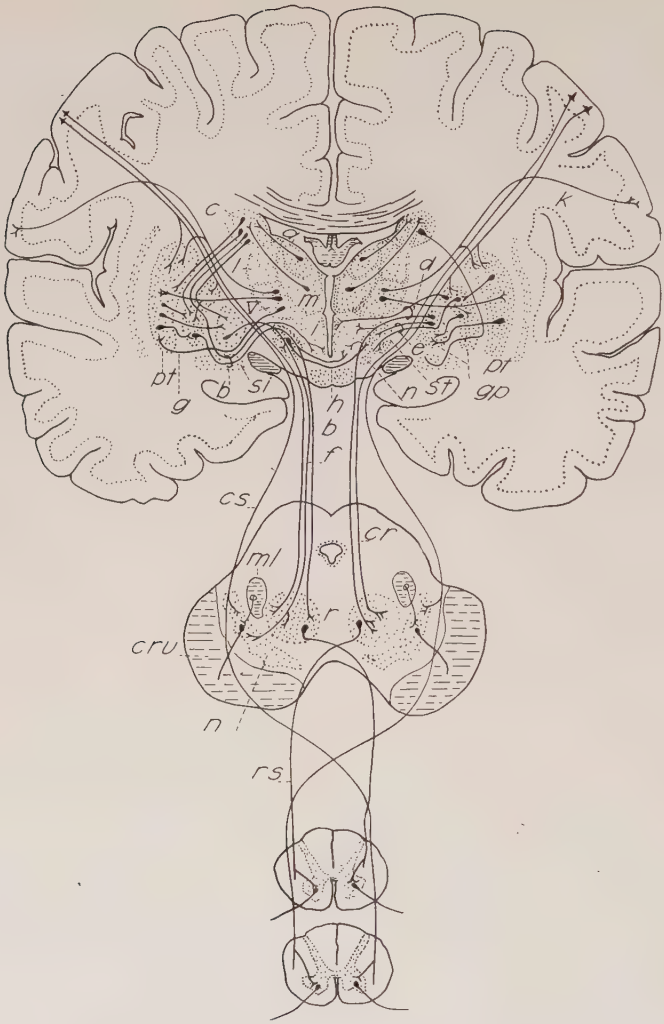

Fig. 47. Thalamostriatal and striothalamic conduction pathways: *a*, anterior thalamic nucleus; *b*, ansa lenticularis; *c*, caudate nucleus; *cr*, corticorubral tract; *cru*, crura; *cs*, corticospinal tract; *d*, lenticular fasciculus of Forel; *e* and *f*, fasciculus striosubthalamicus; *g*, part of ventral thalamic peduncle; *gp*, globus pallidus; *h*, commissural connections of nucleus subthalamicus by way of supramammillary commissure; *i*, zona incerta and fields of Forel; *k*, thalamocortical radiations to postcentral gyrus; *l*, lateral thalamic nucleus; *m*, median thalamic nucleus; *ml*, median lemniscus; *n*, substantia nigra; *pt*, putamen; *r*, red nucleus; *rs*, rubrospinal tract; *si*, substantia innominata; *st*, nucleus subthalamicus; *v*, ventral thalamic nucleus.

modify the responses from the cortex, so the cortical centres modify and direct and in certain cases inhibit responses from the medial division. In part this is effected through corticothalamic fibers which pass directly to these medial nuclei, and in part it is accomplished through the action of efferent cortical paths on the efferent centres of the subthalamus, bulb and spinal cord through which these nuclei may discharge nerve-impulses.

For purposes of discussion, the lateral division of the dorsal thalamus may be divided into two groups. To one of these groups may be allocated those centres which are primarily nuclei of termination for the ascending secondary sensory paths, such as the medial and lateral lemnisci and the optic tract. Such centres are the centromedian nucleus, the ventral nucleus, the posterior nucleus, the pulvinar and the medial and lateral geniculate nuclei. These nuclei develop along with the projection centres of the cerebral cortex, and the distinctness with which the various groups of impulses are delimited within them is reflected in the specificity of the cortical projection centres. Thus the optic and auditory cortical centres can be distinguished sharply from other sensory projection centres, just as their thalamic nuclei are clearly definable from other thalamic areas, while the pain, temperature and tactile impulses, which are not so definitely localized with respect to each other in the diencephalon, are discharged into a single, general cortical area. The nuclear groups within the ventral nucleus are looking forward to such a localization, for cortical localization must always have its basis clearly defined in the dorsal part of the diencephalon. The ventral nucleus is phylogenetically old. The nucleus rotundus of lower forms appears to the authors to be its precursor, as Ingvar (30) and others have also thought, and not the forerunner of the medial nucleus, as is sometimes believed. It is significant that in lower mammals it retains its primitive form, and that it is only in higher mammals and in primates, in which the pattern of cortical localization specific for these forms is established, that the ventral nucleus attains its greatest differentiation. This is further evidenced in the relation existing between the development of the dorsal nucleus of the lateral geniculate nucleus and the elaboration of the cortical optic centres. For while the ventral part of the lateral geniculate nucleus is represented in nearly all submammalian forms from fishes on, the dorsal nucleus is phylogenetically of much later development, being only meagerly represented

in reptiles, not attaining its full nuclear pattern until higher mammalian forms are reached; consequently, the number of projection fibers to the forebrain from the optic thalamic centres is relatively small in most submammalian forms and increases *pari passu* with the increase of the dorsal geniculate nucleus.

The centromedian nucleus has a significant location, situated as it is between the ventral and the medial nuclei of the thalamus. The majority of workers on lower mammalian forms have placed it with the medial group. Certain of the observers who have studied higher forms have relegated it to the lateral division of the thalamus. Just as it is intermediate in position, so it is intermediate in its connections. It is in close synaptic relation with the nuclei of the midline and the medial nucleus, and thus presents certain of the functional characteristics of the medial group. It resembles the ventral nucleus of the lateral division in being a major region of termination of secondary ascending paths. It is of particular interest to note that of these ascending paths, those carrying pain (lateral spinothalamic and trigeminal fibers) and possibly general sensibility, enter into synapse in part in the centromedian nucleus. Some few lemnisci fibers are said to reach the medial nucleus (Probst (43–45)). The question arises whether it is possible to hypothecate that this centre will be involved in thalamic consciousness of pain. There is within the lateral division of the dorsal thalamus a group of nuclei not concerned primarily with the reception of ascending sensory impulses and their transmission to cortical projection centres. Of this group the lateral nucleus is the most typical representative. Beginning apparently as a single nuclear group in lower mammals, it increases in size and in differentiation with the advance in the mammalian scale and reaches its highest differentiation in primates. Inadequate knowledge of the thalamic relations of the lemnisci makes it uncertain whether they are main determining factors in its development, while its connection with the association centres of the cortex postulates that it develops progressively with the later cortical areas. Thus in any mammalian form, the ventral nucleus develops and differentiates with the projection centres, while the lateral nucleus probably differentiates with the association centres. What other factors may have a rôle to play in the development of the lateral nucleus it is not at present possible to state. However, it should be emphasized that the lateral division of the thalamus has portions which are phylogenetically so old that if a division

into paleothalamic and neothalamic centres is to be made, it cannot be done on the basis that the medial thalamus is phylogenetically older than the lateral thalamus, for both medial and lateral divisions contain paleothalamic and neothalamic constitutents.

The account given indicates that the dorsal thalamus is on the afferent side of the arc. Quite as definitely the ventral thalamus or subthalamus is concerned in the transmission of efferent impulses. It receives impulses from four major areas, namely, the cortex, the striatum, the dorsal thalamus and to some extent the hypothalamus. The cortical connections are by way of collaterals from corticobulbar and corticospinal and probably corticorubral paths, and through stem-fibers enter into synapse in the zona incerta and adjacent gray matter, in the substantia nigra and in the red nucleus. The major striatal connections of the subthalamic area are by way of the dorsal, medial and ventral divisions of the ansa lenticularis (von Monakow (38)). The most dorsal of these, after passing directly through the posterior limb of the internal capsule, supplies the fields of Forel, the periventricular gray matter, and sends fibers to the red nucleus. The medial division distributes fibers to the subthalamic region, the red nuclei and the substantia nigra. This medial division likewise passes through the internal capsule, but the ventral division is sublenticular in its course, being a part of the ansa peduncularis. This ventral division terminates in the red nucleus and in the field of Forel of the same and of the opposite side, after decussation in the supramammillary commissure. In view of the significant work of Ramsay Hunt (29) and others on the importance of the striatum in the control of automatic associated movements, the striatal paths here enumerated are deserving of special consideration. A knowledge of these paths is due to the painstaking work of Forel (16), Déjerine (11) von Monakow (38) and others. It is evident that such subthalamic paths as those described, from the cortex and striatum, indirectly afford pathways of discharge for the dorsal thalamic centres. Reference should be made to Figure 47 in which the connections of the dorsal thalamus with the subthalamic centres are indicated. The dorsal thalamus and the hypothalamus as well, through their connections with the zona incerta, may discharge nerve-impulses directly to the motor centres of the bulb, through the thalamobulbar and thalamoolivary paths, and to the tectal and tegmental centres, including the red nucleus, by means of the incertotectal and incertotegmental paths.

This connection makes possible the simpler thalamic reflexes. It must be evident from this account that the thalamus is much more than a gateway to the cortex; it is an exceedingly important reflex centre and a centre involved in affective tone.

One of the aims of the foregoing presentation has been to indicate the gaps in the knowledge of thalamic connections, and particularly of those concerned with the mediation of visceral sensibility. It will be noted that no definite paths have been traced from the visceral centres of the spinal cord and the lower part of the medulla to the thalamic centres. Suggestions as to possible paths for these impulses are found scattered through the literature, but these are sadly in need of further confirmation. It is possible that the general visceral afferent impulses are carried to the diencephalic centres by non-medullated fibers, or even more probably by a chain of neurones similar to those associated with the lateral spinothalamic path (Fig. 44). Further analysis of the periventricular fiber system, particularly in its relation to the periventricular gray matter in the diencephalon and mesencephalon and its relation to the tegmental nuclei and other efferent centres, would be of great value for an understanding of the discharge paths of the visceral areas of the diencephalon. This system undoubtedly involves, in part, chains of neurones rather than uninterrupted neurone paths.

It is to be remembered that the primitive conducting pathways of the nervous system are in the form of a series of neurones, comparable to links in a chain. With the need of greater specificity and speed of conduction, these neurone chains are replaced during phylogeny and sometimes during ontogeny, as in amphibians (Herrick and Coghill (25)), by longer conducting elements which may carry impulses without synapse for considerable distances. The main conducting paths of the higher vertebrate nervous system are made up of such neurones. It would, therefore, seem altogether probable that the less highly specialized general visceral sensibility may be carried forward at least in part by such neurone chains. It is evident that such a pathway would not be capable of demonstration by the ordinary methods of experimental degeneration. Further work is likewise needed on the details of the localization of the lemnisci fibers within the ventral nucleus. Moreover, there is no clear understanding of the details of thalamocortical and corticothalamic connections outside of those related to the projection centres; and the thalamostriatal connections

are frequently confused with thalamocortical and corticothalamic paths. These problems are all deserving of further investigation. A study of the details of the origin, course and termination of the thalamobulbar, thalamo-olivary and associated descending paths, is needed for a more complete understanding of thalamic reflexes.

If the foregoing discussion has contributed to an understanding of the complexity of the diencephalon, as evidenced in phylogeny and ontogeny, and has given a greater appreciation of the problems involved, one of the purposes of this contribution will have been attained (28).

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CHAPTER XI

THE HYPOTHALAMUS AND THE SYMPATHETIC NERVOUS SYSTEM[1, 2]

J. BEATTIE, M.D., G. R. BROW, M.D., AND C. N. H. LONG, M.D.

Part One

THE DEPENDENCE OF THE EXTRASYSTOLIC ARRHYTHMIA OF THE HEART PRODUCED BY CHLOROFORM, UPON THE INTEGRITY OF THE SYMPATHETIC NERVOUS SYSTEM; AND THE USE OF THIS ARRHYTHMIA AS AN INDICATOR OF SYMPATHETIC ACTIVITY

I. Introduction
II. Review of Goodman Levy's Work on the Cardiac Arrhythmias Produced by Chloroform Anesthesia
III. The Authors' Work, Showing the Effects of the Extirpation and Stimulation of the Sympathetic Nervous Pathways on the Arrhythmias Produced by Chloroform Anesthesia
IV. The Persistence of Extrasystoles under Chloroform Anesthesia
V. The Effects of the Injection of Adrenalin on the Heart under Chloroform Anesthesia
VI. The Abolition of Extrasystoles by Decerebration
VII. The Effects of Extirpation of the Stellate Ganglia
VIII. The Effects of Stimulation of the Stellate Ganglia
IX. The Effects of Section of the Thoracic Roots within the Spinal Canal
X. The Effects of Stimulation of the Thoracic Nerves within the Spinal Canal
XI. The Determination of the Level of Section in the Brain Necessary to Abolish Extrasystoles

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[1] From the Department of Anatomy, McGill University, and the University Medical Clinic, Royal Victoria Hospital, Montreal.

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The authors are also indebted to the Council of the Royal Society of London for their kind permission to reproduce Figures 56–60 and 71–76. These, together with certain portions of the subject matter, originally appeared in the Proceedings of the Royal Society, Series B, 1930.

XII. The Effects of Stimulation of the Hypothalamic Region under Chloroform Anesthesia
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INTRODUCTION

THE conception of the autonomic nervous system as usually set forth in anatomical and physiological text-books, has remained almost unchanged for many years. In these works, there is little or no reference to the possible existence of controlling or correlating mechanisms for the sympathetic nervous system within the brain-stem and spinal cord.

Evidence has, however, been accumulating slowly that certain regions of the brain and brain-stem will, on stimulation, produce phenomena of an undoubted sympathetic character. Furthermore, experimental or clinical lesions of these areas are followed by symptoms of either sympathetic stimulation or deficiency.

The Hypothalamus and Carbohydrate Metabolism

Claude Bernard (13) showed that piqûre of the medulla was followed by glycosuria, which did not occur if the splanchnic nerves had been previously cut (Aschner (3-5), Camus and Roussy (19)). Sachs and MacDonald (54), Bailey and Bremer (6), have shown that experimental lesions of the hypothalamus are followed by glycosuria and hyperglycemia of sympathetic origin. Camus, Gournay and Le Grand (19) produced a glycosuria lasting six weeks, by means of lesions of the paraventricular nucleus of the hypothalamus.

The relation of the glycosuria following these lesions in the hypothalamus to the pituitary gland has been and still is a subject of controversy. Certain workers (Cushing (25)) are of the opinion that such a glycosuria is always due to injury of the pituitary gland, while others claim that the hypothalamic lesion is the essential one. The general concensus of opinion seems to be that injury and irritation of the hypothalamus is the fundamental cause of the glycosuria and the hyperglycemia.

The Hypothalamus and the Cardiovascular System

Karplus and Kreidl (37, 38) have shown that the stimulation of the hypothalamus in a well-localized region, is followed by pressor effects

and an increase in the rate and force of the heart-beat. These effects are due partly to the reflex secretion of adrenalin, as has been demonstrated by the skilful experiments of Houssay and Molinelli (31).

The Hypothalamus and Temperature Regulation

The sympathetic nervous system plays a large part in the regulation of the temperature of the body by its control of the sweat-glands and possibly by other mechanisms. The puncture of the floor of the third ventricle of the brain in the region of the tuber cinereum is usually followed by hyperthermia (Barbour (8–10), Isenschmid and Krehl (35), Citron and Leschke (23), Barbour and Wing (11), and Isenschmid and Schnitzler (36)).

The Hypothalamus and Polyuria

Puncture of the hypothalamus in the region of the floor of the third ventricle is followed by the condition of diabetes insipidus. This was believed at one time to be due to the disturbance of the pituitary gland. Bailey and Bremer (6), Camus and Roussy (20), have shown conclusively that the essential lesion is one of the hypothalamus. Whether this phenomenon is of direct sympathetic origin or whether it is due to disturbances in purine metabolism as a result of the puncture, is not at present settled. The nuclei involved in this occurrence have been worked out by Raminez-Corria (52). Bourquin (14), Le Breton and Kayser (40), and Camus and Gournay (17) have also published papers on this subject.

The Hypothalamus and Ocular Phenomena

Indications of sympathetic activity are easily followed in the pupil. The stimulation of the superior cervical sympathetic ganglion is followed by dilatation of the pupil, bulging of the eyeball, and retraction of the nictitating membrane. Karplus and Kreidl (37, 38) have shown that the same effects are produced by the faradic stimulation of the hypothalamus.

The Hypothalamus and the Pilomotor System

The erection of the hairs in fur-bearing animals is a result of sympathetic stimulation. Brown and Sherrington (15) have demonstrated that the stimulation of the ventral region of the midbrain close to the lateral edge of the central gray matter of the aqueduct at the level of the inferior colliculus, is followed by the erection of hair,

lashing of the tail, unsheathing of the claws, and a rise in blood-pressure.

The Hypothalamus and the Adrenal Medulla

The intimate relation existing between sympathetic excitation and adrenalin secretion has been worked out admirably by Cannon. Along with Rapport (22) he has demonstrated that the reflex discharge of adrenalin from the adrenal medulla does not occur if the brain has been transected at the level of the inferior colliculus. Houssay and Molinelli (31) have, however, demonstrated the existence of higher centres situated in the hypothalamus; and the stimulation of this region is followed by a discharge of adrenalin.

The few instances which have been cited above are sufficient to prove that in the hypothalamus there are situated groups of cells which functionally and anatomically also, as will be shown later, are integral parts of the sympathetic nervous system.

In the first part of this paper, the authors will discuss the relation existing between a certain type of cardiac irregularity produced by chloroform anesthesia and the integrity of the sympathetic nervous connections of the heart. After producing evidence that such irregularities do not occur in the absence of sympathetic connections to the heart, the authors will then demonstrate the existence of higher centres in the neuraxis, by using the cardiac irregularities as indicators of the integrity of the sympathetic connections to the heart. In the second part, the anatomical investigations are presented. Here the evidence is built up from the experimental work outlined in Part One, and in addition from the results of lesions observed in the hypothalamus. The degenerations following such lesions are traced, and the relationship of these degenerations to the lower sympathetic centres is established.

REVIEW OF GOODMAN LEVY'S WORK ON THE CARDIAC ARRHYTHMIAS PRODUCED BY CHLOROFORM ANESTHESIA

In a series of papers Levy (41–43) showed that cats under chloroform anesthesia were very likely to develop extrasystoles of varying types, especially when the concentration of vapor was 2 per cent or less. The extrasystoles were of all grades, from isolated ectopic beats to complete tachycardia of the ventricles. Levy and Lewis (44) were of the opinion that this tachycardia passed readily into ventricu-

lar fibrillation. When the concentration of the chloroform vapor was greater than 2 per cent, the frequency of the appearance of abnormal ventricular beats was lessened, but with a vapor concentration of 0.5 per cent, the frequency of ventricular fibrillation was increased.

Levy did not make any observations on the appearance of cardiac irregularities under other anesthetics without accessory stimulation. The authors will point out later that extrasystoles, but not ventricular fibrillation, can arise spontaneously under ether and di-allyl-barbituric anesthesia. Levy also found that when adrenalin was injected into cats under light chloroform anesthesia, extrasystoles and ventricular fibrillation appeared within a few seconds. The dose used was 0.065 mg., and the method of injection was intravenous. This observer showed that the lighter the anesthesia, the more readily did ventricular fibrillation appear after adrenalin injection; but that with all concentrations of the vapor, extrasystoles were observed. He stated that, in pithed cats with the brain destroyed and no chloroform administered, the heart remained regular when adrenalin was injected; but that, when 0.5 per cent chloroform was applied, the heart could be made to fibrillate on the injection of 0.065 mg. of adrenalin. The production of extrasystoles in the absence of any anesthetic whatsoever is a point on which the authors differ from Levy. He noted that in non-anesthetized animals, irregularities occurred in the blood-pressure tracing, on the injection of adrenalin, but he attributed these variations to movements on the part of the animal. The doses of adrenalin which he used were 0.065 mg. Hume (34) has shown recently that the injection of adrenalin (0.14 mg.) into the veins of normal, healthy men, produced ventricular extrasystoles; and as the authors will show later, they have made confirmatory experiments on non-anesthetized cats. Hence they disagree with the statement of Levy that "adrenalin has no innate power of producing ventricular irregularities, but that it acts as an exciting cause only when the heart is rendered sensitive by chloroform."

Levy (41-43) next showed that the excitation of the stellate ganglia or the accelerator fibers of the heart would produce ventricular tachycardia and ventricular fibrillation in an animal under light chloroform anesthesia. It is of interest to note that when the stellate ganglia were stimulated and the percentage of chloroform was increased, tachycardia still appeared but ventricular fibrillation did not. This

finding, of course, confirms the results of the adrenalin experiments, inasmuch as it shows that some stimulation of the heart or of the sympathetic nervous system is an exciting factor in the production of such irregularities in cats anesthetized by chloroform. The same observer demonstrated that the stimulation of the peripheral end of a splanchnic nerve of a cat, either before or after the extirpation of the stellate ganglia, gave rise to ventricular tachycardia and in some cases to ventricular fibrillation. This effect was immediately abolished when the adrenal glands were removed.

Levy next attempted to stimulate the heart reflexly by cutting or faradizing the sensory nerves. Those which he used were either the central ends of the sciatic or of the splanchnic nerve. When this experiment was performed upon cats under light chloroform anesthesia, extrasytoles were observed. In some animals, ventricular fibrillation occurred. When the stellate ganglia had been extirpated, sensory stimulation still produced the same result. The removal of the adrenal glands alone did not prevent the appearance of cardiac irregularities, when either the sciatic or the splanchnic nerve was stimulated centrally. When both adrenal glands were removed in addition to the stellate ganglia, the heart remained regular under sciatic stimulation.

The conclusion from these experiments was that sensory stimulation under chloroform may accelerate the onset of cardiac irregularities by two mechanisms: (*a*) the reflex stimulation of the heart through the cardiac accelerator nerves; and (*b*) the reflex stimulation of the suprarenal gland.

When the heart is regular under chloroform, the mere cutting of the vagus nerve is sufficient to precipitate the irregularities. The relation of the vagus nerve to these irregularities is complex and must be considered from three aspects. This effect is brought about in one or both of two ways: (*a*) by the sensory stimulation involved by the trauma of cutting, in which case the effect is comparable to that of cutting the sciatic nerve; and (*b*) by the removal of the vagal tone which allows an unchecked effect of the sympathetic nerves on the heart, and thus produces irregularities by a mechanism similar to that brought about when the stellate ganglia are stimulated. The combined effect may be of such a degree that the extrasystolic arrhythmia may progress to ventricular fibrillation. With regard to the third aspect of the result of vagal effects (*c*), Levy makes the following state-

ment, "It is a stimulation of heart function which is the determining cause of ventricular irregularities in a heart already rendered irritable by chloroform. If the above is true, then stimulation of the peripheral end of the vagus should abolish ventricular tachycardia." Levy has shown that this effect can be produced.

When the stellate ganglia are removed and later the adrenal glands are excised, section of the vagus nerve may give rise to cardiac irregularities. This is explained by Levy on the assumption that section of the vagus may give rise to impulses which can call forth the secretion of an adrenalin-like body and so produce extrasystoles. It seems to the authors that it is not necessary to postulate the existence of accessory adrenal glands, or the secretion of adrenalin-like bodies to explain this effect. It has been demonstrated that almost constantly in the cat (Cannon and others (21)), and always in man (Kuntz (39)), there are cardio-accelerator fibers which do not pass through the stellate ganglion. It is possible then that the effect of section of the vagi after the removal of the stellate ganglia is due to an increase in heart-rate produced by these accelerator fibers. Even should these fibers not be in existence in the particular animal, there seems to be no reason to deny that the mere release of the sinus-node from vagal influence may not allow the heart to accelerate and fulfil the conditions necessary to precipitate the irregularities which are postulated by Levy to be (*a*) a rapid heart, (*b*) an increase in ventricular output, and (*c*) a rise in blood-pressure.

In his paper published in 1913, Levy (42) deals with the relation of changes in blood-pressure to the production of irregularities in the heart under chloroform. It is necessary to consider this factor, since all the various stimuli used by him in his previous work produce alterations in blood-pressure. Such changes in the blood-pressure may be brought about by the compression of the large arteries or of the large veins. Hering (30) showed that the compression of the aorta at the arch gave rise to extrasystoles. While the authors admit that the compression of this part of the arterial system occasions pressor effects, these may also be produced by other causes: (*a*) by the stimulation of sensory sympathetic nerve-endings within the wall of the aorta; and (*b*) by the shutting off of the blood-supply to a large part of the brain by the irritation of brain-stem centres during the preliminary phase of asphyxia. It is not possible to separate any one of these factors from another. Although Levy attempted to raise the blood-

pressure by the compression of the abdominal aorta at the level of the celiac artery, he ignored the fact that such compression must certainly irritate the celiac ganglia by the trauma of the operation. Hence, this compression cannot be a pure effect. It can be seen that this method of raising the blood-pressure may give rise to sensory stimulation, by the irritation of the skin of the abdominal wall, which in itself may be enough to produce adrenalin secretion. Furthermore, the secretion of adrenalin due to the traumatizing of the splanchnic nerves must be considered. Levy also raised the blood-pressure level by compression of the aorta through a window in the thoracic cavity. Here again, the intimate relation of the sympathetic nerves to the aorta cannot be ignored. It does not seem possible to regard the rise in blood-pressure produced by this procedure as a pure effect. The cutting off of the blood-supply to the abdomen when the adrenal glands are intact, is known to produce the secretion of adrenalin. Hence the authors feel that these mechanical procedures are of little value. They do not, however, deny that the rise in pressure alone has some effect in predisposing the heart to produce extrasystoles.

The present writers confirm the observations of Levy (41–43) that low blood-pressure, below 100 mm. of mercury, renders the production of extrasystoles very difficult. When the venous inflow of blood to the heart is reduced during a period of arrhythmia, the extrasystoles disappear as the blood-pressure falls. Levy stated that a fall of 10 mm. was sufficient to abolish the extrasystolic rhythm. He also stated that a fall in blood-pressure, caused by a too great inflation of the lungs, would abolish or prevent extrasystoles. The authors have noted only too frequently that this observation is correct, but another factor must be considered. The stimulation of the vagal endings within the lung parenchyma may retard the heart enough to cause the irregularities to disappear. The effects on the extrasystoles of bleeding have been observed by Levy. When the bleeding is sufficient to cause a fall in blood-pressure of 10 mm. or more, the extrasystoles disappear.

The effects produced by asphyxia can be explained by the general stimulation of nerve-tissue, including the sympathetic nervous mechanism. Levy noted that, when an animal was asphyxiated under chloroform anesthesia, irregularities were of common occurrence but fibrillation did not happen frequently. His explanation of these effects is that as a result of the asphyxia, the whole of the sympathetic

nervous system is stimulated, thus having a direct effect upon the heart and the secretion of adrenalin. The resulting conditions are almost ideal for the production of irregularities.

The Action of Drugs

Adrenalin. The action of adrenalin has already been discussed. Its effect is produced by a stimulation of sympathetic motor endings in the heart and in the blood-vessels (pp. 252–253).

Nicotine. The intravenous injection of nicotine in doses of from 5 to 10 mg. in a cat under chloroform anesthesia, produces ventricular fibrillation or ventricular tachycardia. This drug acts upon and stimulates the peripheral sympathetic ganglia and, in addition, accelerates the secretion of adrenalin (Houssay and Molinelli (33)). The first effect of nicotine is to produce a fall in blood-pressure, with a slowing of the heart. When the heart is irregular before the injection of the drug, this preliminary effect leads to the abolition of the extrasystoles, but, as the blood-pressure commences to rise, the extrasystoles reappear. This result is occasioned by transitory stimulation of the vagal ganglia. When the stellate ganglia and adrenal glands are removed, the injection of nicotine into a vein may cause the appearance of a few extrasystoles. The explanation by Levy, that the nicotine causes the secretion of adrenalin from accessory adrenal glands, is probably inaccurate on the grounds already advanced (see p. 255). Where cats had been pithed and the brain destroyed, the injection of nicotine produced a rise in blood-pressure and the development of irregularities in some of the animals. This result is analogous to the effect obtained by the authors by the injection of adrenalin in large doses in decerebrated animals. It would appear then, that exceedingly strong sympathetic stimulation, even in the absence of chloroform, may lead to the production of irregularities. This is a similar effect to that seen when adrenalin is injected into normal human beings (Hume (34)). Levy has, therefore, concluded that the nicotine effect is due not only to the pressor action of the drug, but also to the stimulation of the sympathetic nerve-supply to the heart.

Strychnine. When this drug is injected, it produces an effect on the somatic and sympathetic synapses within the neuraxis. Among other reactions, there is a great rise in blood-pressure and an acceleration of the heart. While a certain part of the rise in blood-pressure may be

owing to the muscular convulsions, yet on the administration of curari, the pressor effects still occur. In cats under chloroform anesthesia, the injection of the drug is followed by ventricular fibrillation. This is due to the violent sympathetic discharge of nerve-impulses. The removal of the stellate ganglia, while preventing ventricular fibrillation, does not prevent the occurrence of the irregularities. They must, in this case, be due to the discharge of adrenalin, for when the adrenal glands and the stellate ganglia have been removed, the extrasystoles do not appear. The injection of the drug causes almost as great a rise in blood-pressure after both the adrenal glands and stellate ganglia have been removed, although the heart remains regular. This result illustrates the relatively small importance of a pure pressor effect in the absence of other influences acting upon the heart.

Barium chloride. The effects of barium chloride on the heart have been studied extensively (53, 55). Rothberger and Winterberg (53) were able to produce irregularities by sympathetic stimulation or by the use of adrenalin in animals which had received previously a small dose of this drug. In this respect, the drug acts in much the same way as chloroform, and in fact will itself produce ventricular fibrillation in a cat anesthetized with ether. Barium chloride is known to be a powerful vasoconstrictor agent; and it is quite possibly a general sympathetic stimulant, since there is some evidence to show that it influences the secretion of adrenalin. Levy demonstrated that in pithed cats, the injection of the drug without any anesthetic will produce extrasystoles. Furthermore, when the drug is given in small doses with chloroformanesthesia, the heart can be made to fibrillate by simple section of the vagus or by stimulation of the stellate ganglion or by the injection of adrenalin.

Apocodeine. It is known that this drug paralyzes the sympathetic nerve-endings. When it is injected into the vein of an animal showing these irregularities, the extrasystoles disappear and the blood-pressure falls.

Glycolic acid. Glycolic acid acts in a very peculiar manner, since at one and the same time it stimulates the vasoconstrictor centre and dilates the heart and blood-vessels. When injected into the carotid artery of a cat under chloroform, irregularities appear. When injected into a vein, the heart becomes slow, the blood-pressure falls, and irregularities, if present, disappear.

Summary of Levy's Work

The general conclusions from the work of Levy, can be summarized as follows:

1. The appearance of irregularities under chloroform is due to sympathetic stimulation acting on a heart rendered "irritable" by this anesthetic. The stimuli in the absence of chloroform are, as a rule, not sufficient to precipitate cardiac irregularities, although exceptions to this are noted.

2. When spontaneous irregularities are not present, they may be elicited by sympathetic stimulation of a direct or of a reflex nature. This stimulation may be produced by adrenalin, nicotine, strychnine, barium chloride, or asphyxia.

3. The effect of the vagus nerve upon these irregularities must be considered according to the dual nature of this nerve. Stimulation of its peripheral end leads to a slowing of the heart and the abolition of extrasystoles, when these are present. Stimulation of the central end, by reason of the sensory fibers in the nerve, may cause results similar to those produced by the stimulation of a sensory nerve in any part of the body. Lastly, the section of both vagi may lead to a relative stimulation of the sympathetic nerves by the release of the heart from vagal tone.

4. As a general rule, it would seem that any factor which causes acceleration of the heart or an increase in blood-pressure leading to increased work on the part of the heart, predisposes it to the development of irregularities under chloroform. Any agent which decreases the rate or work of the heart by altering these factors, will tend to abolish such irregularities. Irregularities are, therefore, abolished by stimulation of the peripheral end of the vagus, by a large hemorrhage or by the injection of any drug which paralyzes the sympathetic nervous system in any part of its course.

THE AUTHORS' WORK SHOWING THE EFFECTS OF THE EXTIRPATION AND STIMULATION OF THE SYMPATHETIC NERVOUS PATHWAYS ON THE ARRHYTHMIAS PRODUCED BY CHLOROFORM ANESTHESIA

This phase of the investigation had its origin in the chance observation that decerebration abolished extrasystoles when these had been induced by chloroform.

Experimental Methods

Animals. About two hundred cats were used in these experiments. They were prepared for operation by starvation for twenty-four hours previously.

Anesthetics. The anesthetic chiefly employed was chloroform, since this drug is by far the most potent in the production of cardiac irregularities. In the preliminary operative work, e.g. the removal of the adrenal glands, the decerebration, or the exposure of the spinal cord, the authors used either a di-allyl-barbituric acid, urethrane mixture or ether anesthesia. The chloroform was administered in the following manner:

In a large Douglas bag of 100 or 150 liters' capacity, was placed a mixture of oxygen and carbon-dioxide in the proportion of 95 volumes of oxygen to 5 volumes of carbon-dioxide. Enough liquid chloroform was added to bring the mixture up to the required concentration of chloroform vapor (8 cc. of chloroform in 100 liters of gas mixture gives approximately a 2 per cent concentration of chloroform vapor). The anesthetic was administered to the animal by attaching a pair of respiratory valves to the tracheal tube. These valves were made from sausage skin after the manner described by Macleod (46). The outlet from the Douglas bag was attached to the inlet valve and the natural respiration of the animal drew the chloroform into its lungs.

In certain of the experiments in which it was necessary to open the thorax, a respiration pump was employed.[3] The volume of air for insufflation was carefully adjusted, since it is very difficult, or impossible, to obtain extrasystoles in the presence of over-inflation of the lungs,—probably owing to the stimulation of the vagus endings in the lung or to the obstruction of the venous return to the heart. The chloroform vapor was delivered to the animal in these experiments, by attaching the outlet of the Douglas bag to the inlet of the pump. In this way the vapor was then drawn through from the bag into the lungs of the animal. Care was taken to remove as far as possible all grease or oil from the pump, and to replace these lubricants with a layer of graphite.

Blood-pressure. The blood-pressure was recorded by a mercury manometer. The cannula was placed either in the carotid or in the femoral artery. As an anticoagulant, a 2 per cent solution of sodium carbonate was used.

Electrocardiographic tracings. In most of the experiments, simultaneous electrocardiographic tracings were taken at the same time as the blood-pressure records. Such tracings are exceedingly important, since those of blood-pressure alone are very misleading in the interpretation of cardiac irregularities, especially when a slow-moving drum is used. The usual standard Lead 2 was employed in all experiments. The electrodes used were copper discs, sewed beneath the skin of the right forelimb and the left hind-limb. In this way the effects due to alterations in skin resistance were completely eliminated. The electrocardiograph used was the Cambridge-Einthoven model.

The standardization for all curves was 3 mv., which caused a deflection of the fiber of 3 cm. The time marker on all tracings recorded fifths and twenty-fifths of a second.

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[3] The pump used was the "Ideal" pump, made by Palmer of London.

Oxygen saturation of the blood. Buckmaster and Gardner have shown (16) that there is a fall in the oxygen saturation of the blood during chloroform anesthesia. They used varying mixtures of chloroform in air. They were of the opinion that the gradual fall was due to the specific effect of the chloroform on the red cells. The present authors, however, have demonstrated that this explanation is not correct. They consider that the fall in the oxygen saturation of the blood was due probably to the respiratory depression under the anesthetic. In their own experiments, they found that with a mixture of oxygen and carbon-dioxide in the proportions of

TABLE II

OXYGEN SATURATION OF THE BLOOD UNDER CHLOROFORM ANESTHESIA

CAT NO.	DURATION OF ANESTHESIA	OXYGEN SATURATION OF THE BLOOD	OXYGEN CAPACITY OF THE BLOOD
A. CHLOROFORM IN AIR			
	minutes	*per cent*	*volumes per cent*
21	52	Start 85 End 61.8	14.6
22	100	Start 91 End 69	15.1
25	37	Start 82 End 40	16.6
26	96	Start 83.5 End 79.2	16.3
B. 2 PER CENT CHLOROFORM IN 95 PER CENT OXYGEN AND 5 PER CENT CARBON-DIOXIDE MIXTURE			
28	90	Start 91 End 98	13.7
29	101	Start 83 End 98	19.3
31	134	Start 85 End 95	19.3

95 parts of oxygen to 5 parts of carbon-dioxide, it was possible to keep up an efficient respiratory exchange and at the same time maintain the oxygen saturation of the blood at between 90 and 100 per cent. The Van Slyke method was used in the determination of the oxygen saturation.

Blood-chloroform. The authors have made a number of determinations on the concentration of the chloroform present in the blood at the time of the appearance of extrasystoles. The method used was that of Nicloux (48), with slight modifications.

The mean chloroform concentration at the time of the appearance of spontaneous

extrasystoles was 24.2 mg. per cent. The anesthetic dose as determined by Buckmaster and Gardner (16) in cats was 14 to 28 mg. With this amount of chloroform in the blood, the anesthesia corresponds to good "surgical anesthesia."

The figures given in Table III indicate that when this mean amount of chloroform is present in the blood, the concentration is sufficient to render the heart "irritable." The extrasystoles will then appear or, if not present, they can be readily induced by suitable stimulation.

PERSISTENCE OF EXTRASYSTOLES UNDER CHLOROFORM ANESTHESIA

When extrasystoles have been developed under light chloroform anesthesia, the irregularity tends to persist as long as the experimental

TABLE III

BLOOD-CHLOROFORM AT THE TIME OF APPEARANCE OF EXTRASYSTOLES

CAT NO.*	LENGTH OF TIME OF INHALATION OF VAPOR WHEN EXTRASYSTOLES FIRST APPEARED	BLOOD-CHLOROFORM	
	minutes	*mg. per 100 cc.*	
21	7	20.4	
25	10	20.9	
26	22	28.9	
27	79	28.4	
28	20	28.5	Mean 24.2
30	20	33.6	
31	18	16.5	
34	7	17.3	

* The animals were anesthetized with "dial" (di-allyl-barbituric acid and urethane mixture). When full anesthesia was obtained, they were allowed to breathe 2 per cent chloroform in a mixture of 95 per cent oxygen and 5 per cent carbon-dioxide.

conditions are not varied. The oxygen saturation of the blood must be kept constant. The respiratory rate and volume must also be controlled.

The authors have been able to maintain extrasystoles under chloroform anesthesia for ninety minutes, by keeping all the above factors constant (Figs. 48 and 49).

THE EFFECTS OF THE INJECTION OF ADRENALIN ON THE HEART UNDER CHLOROFORM ANESTHESIA

Levy (41–43) has pointed out that the injection of adrenalin (0.065 gm.) into an animal under light chloroform anesthesia leads to ventricular fibrillation. Prior to the appearance of the fibrillation, the

heart shows an extrasystolic arrhythmia. He has stated that, in his experience, the injection of adrenalin into non-anesthetized animals did not produce any irregularity. This is contrary to the authors'

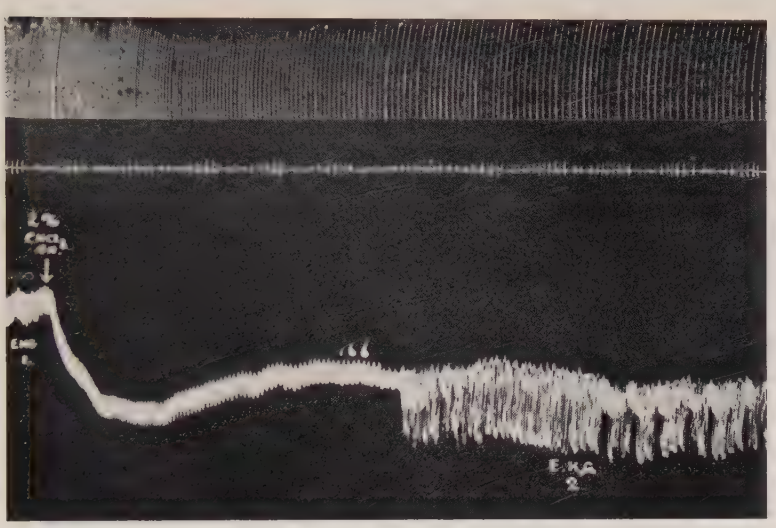
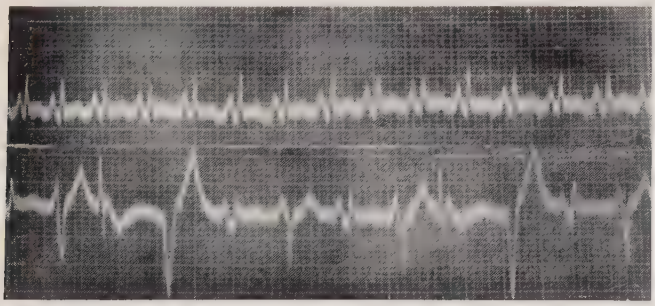


FIG. 48. Blood-pressure tracing showing the effect of 2 per cent chloroform vapor on the rhythm of the heart. Note the preliminary fall in blood-pressure, followed by a rise, and the appearance of the extrasystolic arrhythmia. Respirations are shown on the uppermost tracing. The time marker is indicating five-second intervals.



a

b

FIG. 49. Electrocardiographic tracings taken at the same time as those shown in Fig. 48: *a*, the normal rhythm; *b*, left ventricular extrasystoles interspersed with regular beats.

results and to those of Hume (34). While it is true that ventricular fibrillation never appears in non-anesthetized animals, yet there is no doubt that if the dose of adrenalin is sufficiently large, extrasystoles will appear. Figure 50 shows the production of extrasystoles in an animal decerebrated five hours previously, after only fifteen minutes of anesthesia. The dose of adrenalin in this case was 0.5 mg. Perusal of a large number of published tracings of the effect of adrenalin in animals under a variety of anesthetics, demonstrates that these irregularities are of fairly common occurrence, but they are usually overlooked or interpreted as a "vagal slowing," caused by the raised

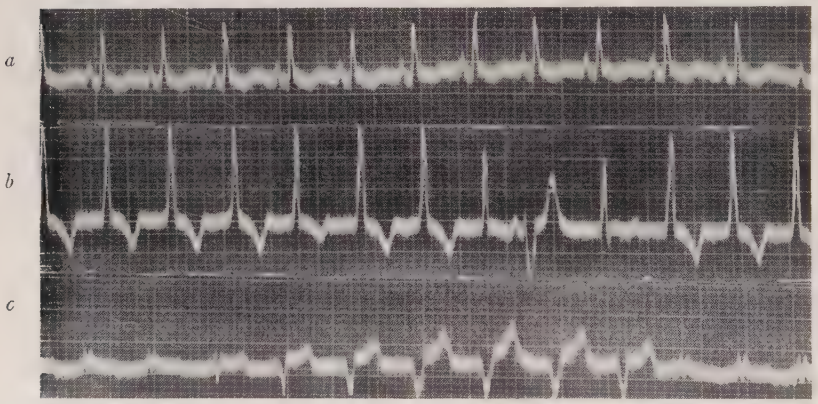


FIG. 50. Electrocardiographic tracings: *a*, normal control rhythm; *b*, right and left ventricular extrasystoles after the injection of 0.5 mg. of adrenalin; *c*, a later curve showing the persistence of the arrhythmia several minutes later.

blood-pressure. A good example of the latter interpretation is seen in a tracing published by Bainbridge and Menzies ((7), p. 461), which shows undoubted extrasystoles. It is quoted here to emphasize the necessity of checking the blood-pressure tracings by electrocardiographic records.

The point of action of adrenalin is on the myoneural junctions of the sympathetic nerve-endings in the heart, and the effect of adrenalin can be interpreted only as a sympathetic stimulation.

THE ABOLITION OF EXTRASYSTOLES BY DECEREBRATION

When an animal has been decerebrated some hours previously and then allowed to inhale the optimum concentration of chloroform vapor

necessary for the production of ventricular extrasystoles, it is found that the abnormal rhythm is not produced. In all their experiments, the authors have always taken care to allow the animal to recover from the shock of the operation and to develop the characteristic decerebrate rigidity before the chloroform vapor is reapplied. Furthermore, if an animal already showing extrasystoles is decerebrated, the abnormal rhythm disappears within a few seconds after the section has been made. The latter procedure is dangerous, for the stimulation of cutting may be sufficient to drive the heart into ventricular fibrillation.

These experiments demonstrate that there must be some mechanism above the level of the Sherrington decerebration, the removal of which will result in the disappearance of extrasystoles induced by chloroform anesthesia.

THE EFFECTS OF EXTIRPATION OF THE STELLATE GANGLIA

Gaskell (27), Pavlov (51) and others have stated that in the cat, the accelerator and augmentor fibers pass into the stellate ganglia by the white rami communicantes of the second, third and fourth thoracic nerves. This statement remained unquestioned until the work of Cannon and others (21) demonstrated that in the same animal, the cardio-accelerator fibers pass from the fifth thoracic nerve, and possibly from even lower levels, into the sympathetic chain from which the postganglionic connections reach the heart through the cardiac ganglia, without communicating with the stellate ganglia. These fibers have been shown by Kuntz (39) to exist in man. However, the greater majority of the accelerator fibers pass into the stellate ganglia by way of the second, third and fourth thoracic nerves on each side.

The present authors have used two different operative approaches to the stellate ganglia. The approach of Anderson (1) was found to be the most satisfactory, since it obviated the use of the respiration pump with all the complicating factors which it introduced. The transpleural approach of Cannon (21) was employed in some experiments, but this method was found unsuitable owing to the necessity of using a pump. After the ganglia had been exposed and the connections carefully isolated, chloroform was applied, and when the irregular rhythm developed, the fibers from the second, third, and fourth thoracic nerves to the ganglia were severed, one at a time. After all the fibers on both

sides had been divided, the abnormal rhythm disappeared. The order of section was not constant. Sometimes the fibers were cut in the order 2-3-4, and at other times, 4-3-2. The latter order was the one most frequently adopted.

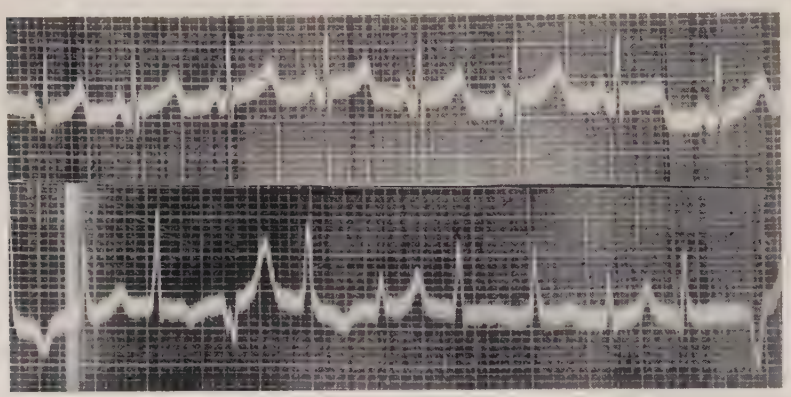


FIG. 51. Electrocardiographic tracings: *a*, the normal control rhythm under light chloroform anesthesia; *b*, the appearance of extrasystoles on painting the stellate ganglia with nicotine (the stimulation phase of nicotine action).

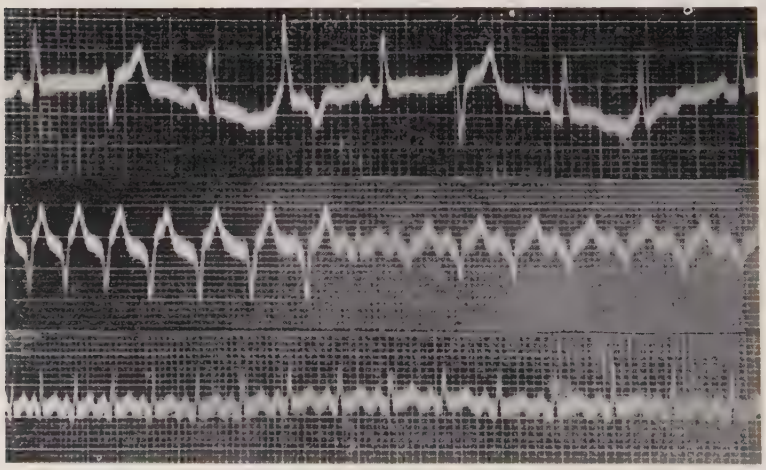


FIG. 52. Electrocardiographic tracings: *a*, extrasystolic arrhythmia in a cat under light chloroform anesthesia; *b*, the arrhythmia commencing to disappear after painting the ganglia with nicotine (the paralytic phase of the nicotine effect); *c*, normal rhythm established (full paralysis of the stellate ganglia).

After the section had been completed, while the ganglia were still attached to the heart by the cardiac nerves, as well as to the cervical sympathetic nerve, their removal had no effect on the rhythm of the heart. When the ganglia themselves were removed, the effect on the cardiac irregularities was the same as when the central connections were cut. The same experiments were repeated with the vagi cut, and in all cases the result was identical. From these observations, it may be concluded that there are fibers in the white rami communicantes of the second, third and fourth thoracic nerves, the section of which

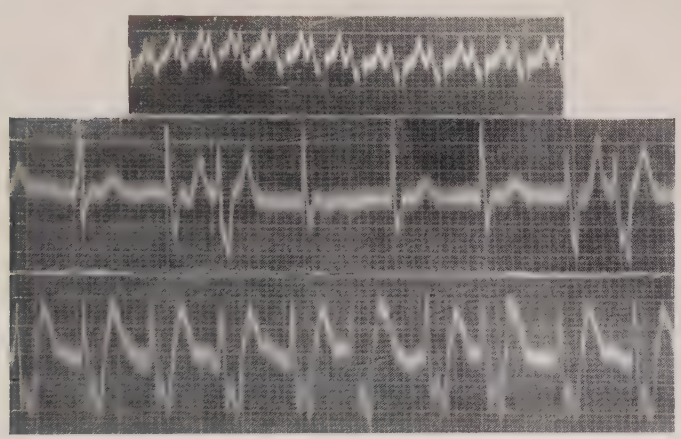


Fig. 53. Electrocardiographic tracings: *a*, normal rhythm under light chloroform anesthesia; *b*, the development of left ventricular extrasystoles upon stimulation of the stellate ganglia; *c*, left ventricular tachycardia (periventricular fibrillation) on the continued stimulation of the stellate ganglia.

leads to the abolition of the abnormal rhythm. The integrity of the stellate ganglion when the central connections are removed, is not in itself sufficient to maintain the irregularity.

Paralysis of the intraganglionic endings by painting the stellate ganglia with nicotine, leads to the abolition of the extrasystoles after a period of excitation when the number of ectopic beats is manifestly increased (Figs. 51 and 52). Levy did not carry out the above experiments but he showed that after the removal of the ganglia, the extrasystolic beats could be called forth only by the reflex secretion of adrenalin or by the injection of this substance into the circulation.

THE EFFECTS OF STIMULATION OF THE STELLAGE GANGLIA

On many occasions Levy (41-43) stimulated the stellate ganglia and the cardiac nerves with a faradic current. He showed that this stimulation under chloroform anesthesia leads at first to the production of extrasystoles and with continued stimulation to ventricular fibrillation. These effects were produced even in the absence of the adrenal glands. The authors have confirmed these results by many experiments and some of their tracings are reproduced in Figure 53.

THE EFFECTS OF SECTION OF THE THORACIC NERVES WITHIN THE SPINAL CANAL

In the following experiments the authors anesthetized the animal with ether or with di-allyl-barbituric acid. When the anesthesia was complete, the spinal cord was exposed in the upper thoracic region by a laminectomy. The animal was then allowed to breathe chloroform vapor.

Since the removal of the stellate ganglia, or section of their central connections, led to the abolition of the cardiac irregularities, it was expected that the section of the proper nerves supplying preganglionic fibers to the stellate ganglia would cause a disappearance of the abnormal rhythm.

As will be shown later, the trauma of section of a sensory nerve will cause a reflex secretion of adrenalin and a maintenance of extrasystoles in an animal whose stellate ganglia have been removed previously. It was, therefore, necessary in these experiments to differentiate between the effects of section of the posterior roots and those produced by cutting the anterior roots. The posterior roots of the second, third and fourth thoracic nerves were cut extradurally. The arrhythmia was markedly accentuated for a short period after the section was made but the extrasystolic arrhythmia did not disappear. The period of accentuation of the abnormal rhythm was lessened considerably when the adrenal glands had been removed before the roots were sectioned. It may be concluded, then, that the integrity of the posterior roots of the second, third and fourth thoracic nerves is not necessary for the maintenance of the extrasystolic beats.

When the effects of the posterior root sections had passed off, the anterior roots of the second, third and fourth thoracic nerves were cut. After section of these on both sides, the arrhythmia disappeared. The trauma due to the section of the anterior roots accentuated for a few

seconds the arrhythmia before the ectopic beats finally disappeared (Fig. 54).

In some animals the adrenal glands were left intact, and the anterior roots were sectioned immediately after the posterior roots. In these, the stimulation from the secretion of adrenalin caused by the trauma of posterior root section, plus the stimulation from the

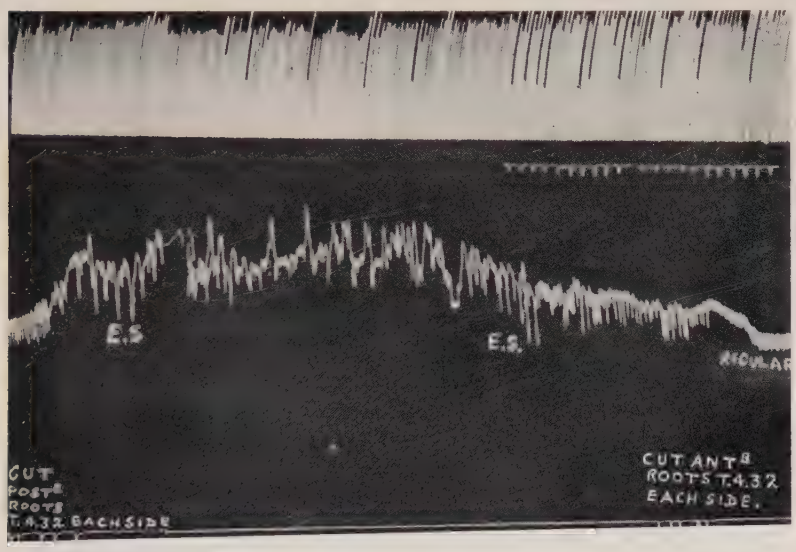


Fig. 54. Blood-pressure tracing showing the effect of section of the anterior and posterior roots of the upper four thoracic nerves within the spinal canal. The posterior root section had no effect on the arrhythmia, but section of the anterior roots abolished this condition. Note that the arrhythmia was not abolished until the last root was severed. The respiratory tracing is uppermost. Time marker is indicating five seconds. The time of section is indicated on the base line. The adrenal glands were removed.

section of the anterior roots, was sufficient to precipitate ventricular fibrillation (Fig. 55). When the adrenal glands are removed, the time taken for the abnormal rhythm to disappear after anterior root section is only a few seconds.

It is possible that section of the nerves in other regions of the thoracic cord might cause identical effects, and that the whole phenomenon of abolition is due to a temporary shock. The authors

demonstrated in one experiment that section of the thoracic nerves was not effective in abolishing extrasystoles (when the adrenal glands were removed) until the level of the fourth thoracic nerve was reached. When this nerve was picked up preparatory to section, it was seen that the arrhythmia was accentuated. The same effect was produced on picking up the second and third nerves. After section of all

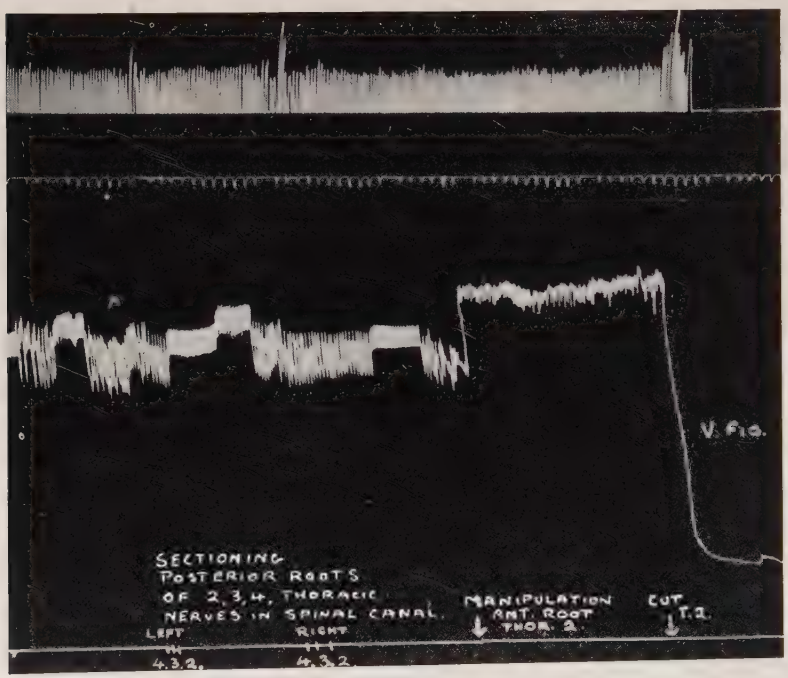


FIG. 55. Blood-pressure tracing showing the effects of section of the roots of the upper thoracic nerves within the spinal canal. The adrenal glands were intact. Note the accentuation of the arrhythmia during the manipulation of the roots. On section of one anterior thoracic root the ventricles fibrillated.

these nerves, the heart became regular. The first nerve was left intact and section of it, after some minutes of regular rhythm, produced no effect upon the heart. The effect on the arrhythmia, therefore, is apparently specific for the second, third and fourth thoracic nerves.

When the lower thoracic nerves were sectioned within the spinal

canal, the blood-pressure curve showed a tendency to rise for a few seconds after each nerve was sectioned. When this preliminary rise passed off, the pressure tended to fall. When the adrenal glands remained intact, the rise was considerable, but if these were removed, the pressor effect was smaller. There is no doubt, then, that the pressor effect caused by section of the lower thoracic nerves is greatly increased by the reflex secretion of adrenalin which takes place.

After eliminating all the accessory factors, such as sensory impulses, adrenal glands, spinal shock and trauma of the nerve-section, definite evidence exists that there are in the second, third and fourth thoracic nerves, a number of fibers, the section of which will abolish the abnormal rhythm.

THE EFFECT OF STIMULATION OF THE THORACIC NERVES WITHIN THE SPINAL CANAL

In the preceding section of this paper the effects of transient stimulation of the thoracic nerves have been discussed. The authors have not attempted to stimulate the anterior or posterior roots within the canal by direct faradization.

The effects of stimulation of the posterior roots due to trauma are similar to those which are produced by the stimulation of a sensory nerve anywhere in the body. These two effects produce an exactly similar result—an accentuation of the arrhythmia. This result is due to two causes: (*a*) a reflex secretion of adrenalin; and (*b*) the stimulation of the sympathetic fibers to the heart by a reflex mechanism. When the adrenal glands are removed, the effects of stimulation due to the trauma of the section of the posterior roots, are very slight.

The effects of section of the anterior roots have already been discussed. The authors have pointed out that the transient stimulation due to trauma differs in no way from the direct stimulation of the stellate ganglia. In one animal, the effect of this trauma was sufficiently strong to produce ventricular fibrillation (Fig. 55).

In one experiment, the animal was anesthetized by di-allyl-barbituric acid, and the heart was regular. When the second, third and fourth thoracic nerves were cut, extrasystoles were observed on the electrocardiograph and on the blood-pressure tracing. This is obviously a stimulation effect. In this experiment, the adrenal glands had

been removed some hours previously. Section of the lower thoracic nerves will, if the adrenal glands are intact, produce extrasystoles under chloroform, provided that the arrhythmia is not present at the time of section. If the arrhythmia is present, it is accentuated. When the adrenal glands are removed, these effects are not produced.

There is obviously no difference between the stimulation of the anterior roots of the second, third and fourth thoracic nerves and the direct stimulation of the stellate ganglion. The stimulation of the anterior roots of the lower thoracic nerves has no effect on the arrhythmia. The stimulation of the posterior roots of all the thoracic nerves is directly comparable to stimulation of the central end of the vagus or to faradization of the central end of the sciatic nerve.

THE DETERMINATION OF THE LEVEL OF SECTION IN THE BRAIN, NECESSARY TO ABOLISH EXTRASYSTOLES

The authors have pointed out in a previous part of this paper (p. 259) that the decerebration of the animal prevents the appearance of the extrasystolic arrhythmia, provided there is no disturbance caused by the injection of drugs or by abnormal sensory stimuli. Furthermore, they have shown that decerebration leads to the abolition of the extrasystoles when these are present.

A series of experiments was performed in order to determine the exact level at which the effective section lay. It was found that the removal of the cerebral cortex, provided the thalamus was left intact, had no effect on the irregularities. When the brain was transected by a cut passing from the anterior edge of the superior colliculus behind to the posterior edge of the optic chiasm in front, no abolition of the extrasystoles occurred, nor had this section any effect on the induction of the arrhythmia by chloroform after the operation had been completed. When another cut was made from the same posterior and dorsal limit to the level of the mammillary bodies ventrally, the extrasystolic arrhythmia disappeared and could not be induced again by the reapplication of chloroform. Sections between these two levels did not abolish the arrhythmia permanently.

Histological examination of the brain after section between the superior colliculus and the optic chiasm, demonstrated that the ventral nuclei of the thalamus were intact, as well as the greater part of the ventral portion of the lateral wall of the third ventricle. Furthermore, the globus pallidus had been removed.

To obtain a more accurate localization of the extent of the effective area, it was necessary to employ different operative procedures. The first method was the transoral approach to the floor of the third ventricle which has been described in detail by McLean (47). By exposing the whole of the ventral aspect of the pituitary gland, it was possible by removing the gland, or even without this procedure, to produce stab wounds into the brain tissue without disturbing to any great extent

the vascular structures in this region. It was essential to prevent damage to the cavernous sinus and the smaller sinuses surrounding the diaphragm of the pituitary fossa. Bleeding from these structures was stopped by the application of muscle compresses. In many experiments, however, medullary hemorrhage supervened since the blood flowed downwards after the external hemorrhage had been controlled. All experiments complicated by this factor were discarded and only those

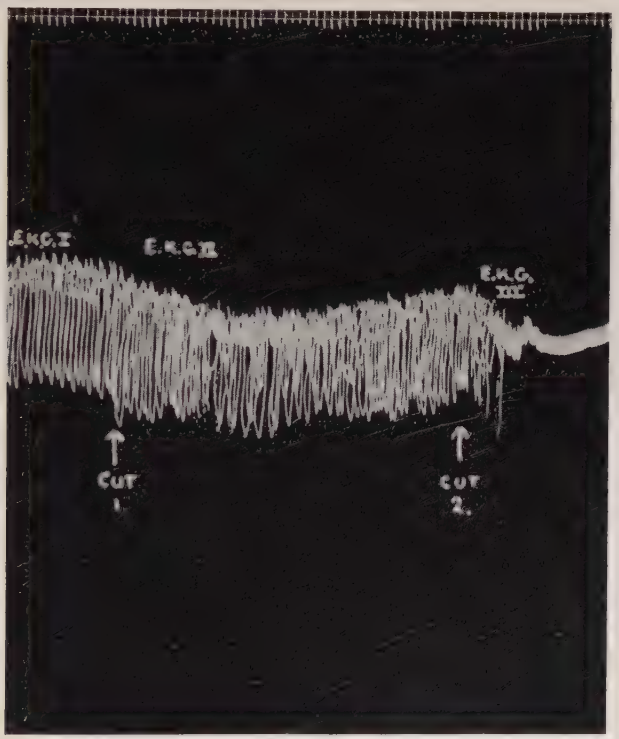


FIG. 56. Blood-pressure tracing showing the effects of section into the hypothalamus. The first section passed anterior to the stalk of the pituitary gland. The second passed through the anterior part of the mammillary body in a plane upwards towards the anterior edge of the superior colliculus.

were retained in which the presence of medullary hemorrhage was proved by autopsy to be absent.

The instrument used was a narrow single-edged paracentesis knife, with a blade 1 cm. in length and 2 mm. in width. It had a sharp point and was guarded 1 cm. from the tip. With this, it was possible to produce unilateral and also complete bilateral lesions. By means of this knife or a piece of "Gillette" razor blade 4 mm.

in width and with a length of unguarded blade of 1 mm. (held firmly in a pair of hemostatic forceps), stab-wounds of a standard depth were made into the floor of the third ventricle at various places. It was found that a wound which passed from below, through or behind the mammillary bodies and upwards in the direction of the anterior edge of the superior colliculus, was effective in abolishing the extra-

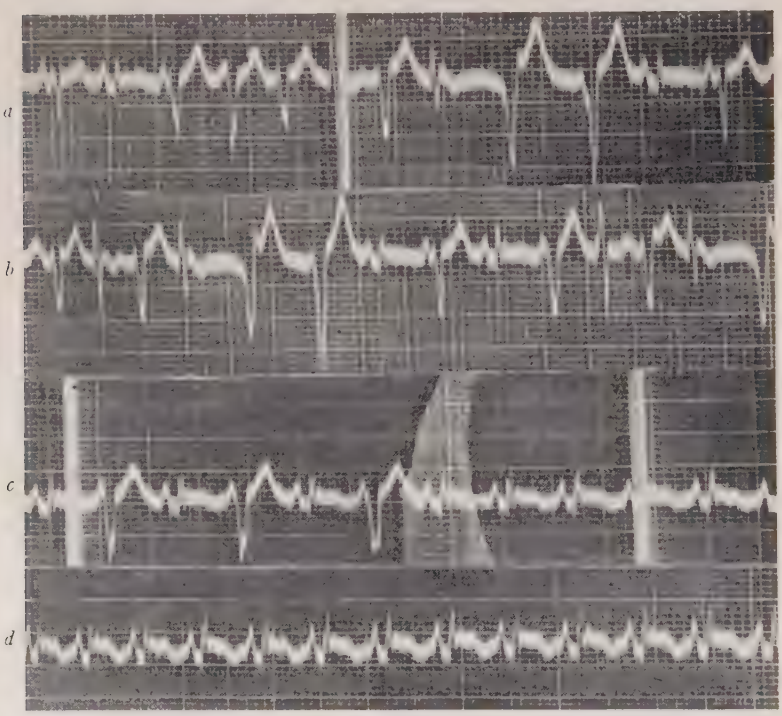


Fig. 57. Electrocardiographic tracings taken during the operation described in Fig. 56: *a*, typical extrasystolic arrhythmia under light chloroform anesthesia; *b*, the persistence of this arrhythmia after the first section anterior to the stalk of the pituitary gland; *c*, the diminution of the arrhythmia and the change to regular rhythm after the second section; *d*, the regular rhythm persisting thirty minutes later, the chloroform anesthesia being continued.

systolic arrhythmia, provided the width of the section was not less than 2 mm. from the middle line on each side. When the section had a width of this magnitude and the animal was allowed to recover, there were no subsequent signs of motor disturbance. Unilateral lesions were of no avail in abolishing the abnormal rhythm, although such lesions were identical in site and depth with the bilateral lesions. The immediate effects of the section are of some interest. The extrasystoles disap-

peared, the blood-pressure remained unchanged, the pupils contracted and did not react to light. In animals allowed to recover, the pupillary constriction was present as a rule only for the first forty-eight hours. The pupils then became normal and reacted to light.

From these experiments it was concluded that the centres involved lay between the levels already indicated and, furthermore, that they lay close to the middle line below the thalamic commissure. Stab-wounds into the brain anterior to the level of the effective stab-wound had no effect on the extrasystolic rhythm. As a control in every experiment (except in the recovery animals) a section anterior to the mammillary bodies was made. It was found that such sections did not disturb the arrhythmia nor affect in any way the blood-pressure level (Figs. 56 and 57). Histological examination demonstrated that the lesion produced lay close to the middle line and never extended as far laterally as the subthalamic body of Luys.

From these observations, a definite region was mapped out with the following boundaries: anteriorly and superiorly, a line joining the anterior edge of the superior colliculus to the posterior edge of the optic chiasm; posteriorly, a line joining the anterior edge of the superior colliculus to the posterior edge of the mammillary bodies; laterally, an imaginary plane not greater than 3 or 4 mm. from the median sagittal plane. Within this region lies a centre, or centres, the removal of which results in the abolition of extrasystoles.

THE EFFECTS OF STIMULATION OF THE HYPOTHALAMIC REGION UNDER CHLOROFORM ANESTHESIA

With the approximate localization determined by the above experiments, the production of extrasystoles was attempted by a direct stimulation of the hypothalamus under chloroform anesthesia, during a period when such irregularities were absent.

Two methods were tried. The first was the direct stimulation of the hypothalamus by the insertion of electrodes through the base of the third ventricle. This method was abandoned, since the localization of the site of stimulation was impossible and the results were therefore inconsistent.

A second method was, therefore, devised which consisted in a hemi-decerebration of the animal, performed under ether anesthesia some hours before the stimulation experiment was attempted. The animal was anesthetized by chloroform during the stimulation. A careful dissection of the lateral wall of the third ventricle was carried out to expose this region in its whole extent. The brain was removed posteriorly as far as the inferior colliculus. By means of bipolar and uni-

polar electrodes, the wall was stimulated, with the results seen in the tracings. Care was taken to prevent the spread of the current. Observations were checked by taking a simultaneous respiratory record and by stimulating the brain in regions as equidistant from the medulla as was this structure from the area stimulated. Upon hypothalamic stimulation, no effect was observed on the respiration. Upon stimulation of the cortex and corpus callosum, no pressor, respiratory or cardiac effects were seen.

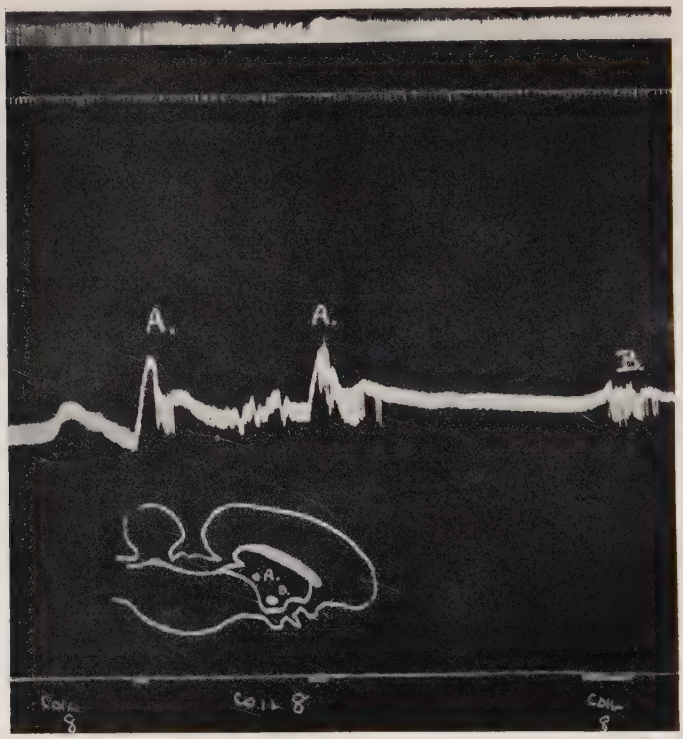


Fig. 58. Blood-pressure tracing showing the effect of stimulation of areas on the lateral wall of the third ventricle in an animal which had been hemidecerebrated. Note the rise in blood-pressure and the production of extrasystoles following stimulation of the areas indicated. The adrenal glands were intact. The respiratory tracing is above and time marker is indicating five-second intervals.

Figures 58, 59, and 60 show the sites of stimulation. Projected on these are the cell-groups as worked out by Winkler and Potter (56), and confirmed by Greving (28) and Foix and Nicolesco (26).

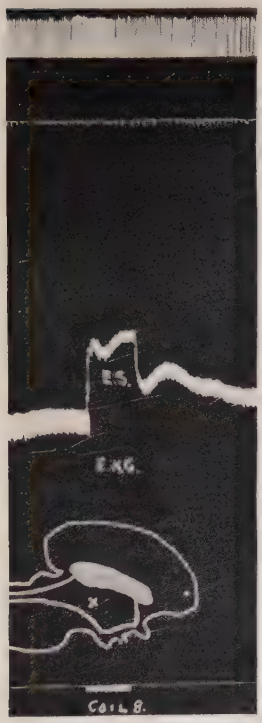


FIG. 59. Blood-pressure tracing showing the effect of stimulation of an area on the lateral wall of the third ventricle. Note the rise in blood-pressure. The respiration curve is on the top of tracing. Time marker is indicating the intervals.

FIG. 60. Electrocardiographic tracing taken synchronously with the blood-pressure curve in Fig. 59, showing the development of the extrasystolic arrhythmia.

The stimulation of Area A (Fig. 58), produces a rise in blood-pressure, accompanied by extrasystoles, after a short latent period. The subsequent fall in blood-pressure is due to the presence of extrasystolic beats. This effect is shown very well in the second stimulation period. Upon the stimulation of Area B, the blood-pressure does not rise appreciably, since the stimulation is followed almost immediately by the extrasystolic beats, which mask the pressor effect. In Figure 59, the stimulation exhibits a marked pressor effect and, in addition to this rise in blood-pressure, there is a decided arrhythmia which does not obscure the pressor effect. Upon the withdrawal of the stimulus, the blood-pressure falls and the extrasystoles disappear. The blood-pressure tracing does not demonstrate the extrasystoles very well but the electrocardiograph confirms their presence (Fig. 60).

Stimulation of other regions of the hypothalamus did not produce rises in blood-pressure or extrasystoles. Only by stimulating along a line from about 3 mm. above the level of the infundibulum to the opening of the aqueduct of Sylvius was it possible to obtain the pressor effect and the extrasystolic arrhythmia.

Karplus and Kreidl (37) have shown that stimulation of the hypothalamus is followed by marked increases in blood-pressure. They approached the region by removing the cerebral cortex and stimulating the region from above. The effect obtained did not depend upon the integrity of the adrenal glands or of the pituitary gland. They showed that section of the splanchnic nerves greatly diminished the pressor effect. The stimulation of the surrounding brain-tissue was not effective in producing blood-pressure changes.

Houssay and Molinelli (31) have demonstrated that, situated around the ventral aspect of the third ventricle are masses of gray matter, the stimulation of which causes a great secretion of adrenalin. By careful technique, they eliminated the possible spread of the current to the medulla. They showed that they could produce the same adrenalin secretion by stimulation of the floor of the fourth ventricle near the middle line.

These experiments, along with those of Cannon and Rapport (22), indicate that there are probably two regions in the brain-stem, the stimulation of which is followed by pressor effects, and adrenalin secretion—one of these is situated in the hypothalamus and the other in the medulla. It must not be forgotten that the effects obtained by medullary stimulation may be due to a stimulation of a direct pathway

from the hypothalamus to the spinal cord. The medullary centre may be an important relay station in the projection pathway from the hypothalamus to the cord. These points will be discussed in Part Two.

The production of extrasystoles by the stimulation of the hypothalamus is due to (*a*) the stimulation of the general sympathetic pathways and (*b*) the stimulation of the paths which are controlling the secretion of adrenalin. When the adrenal glands are removed, stimulation of the hypothalamus still produces extrasystoles. The correlation of these stimulation experiments with the histology of the hypothalamus will also be dealt with in Part Two.

THE EFFECTS OF SENSORY NERVE STIMULATION

Levy has introduced, and the authors have confirmed, the point of view that, in the intact animal under chloroform anesthesia, two mechanisms are at work simultaneously, either one of which alone will allow extrasystoles to appear. He has shown that the stimulation of a sensory nerve will produce extrasystoles when such irregularities had not appeared previously. When either the stellate ganglia had been removed and the adrenal glands left intact, or vice versa, sensory stimulation still continued effective. When both were removed, the sensory stimulation was ineffective (Figs. 61 and 62).

In the authors' experiments, on section of the thoracic nerves (second, third and fourth anterior roots), they found that the integrity of these structures, in the absence of the adrenal glands, still permitted the appearance of extrasystoles; or if these irregularities were not present, they could easily be called forth by sciatic stimulation. The converse is also true. The anterior roots being cut, the mere presence of the adrenal glands was sufficient to permit the appearance of extrasystoles on sciatic stimulation.

When the thoracic cord is cut at the level of the fifth thoracic segment, extrasystoles still appear normally. If they are not present, they cannot under these circumstances be called forth by sciatic stimulation. They can, however, be elicited by the stimulation of the radial nerve. If, now, the thoracic anterior roots are cut, the stimulation of the radial nerve is not effective. If the splanchnic nerve is cut and the peripheral end stimulated, extrasystoles appear. From these observations it may be concluded that the pathway for the reflex secretion of adrenalin is severed by the section of the cord at the level of the

fifth thoracic segment. Again, with the thoracic roots intact and the adrenal glands removed, the stimulation of the sciatic nerve is ineffective when the cord is transected at this level. Sensory stimulation

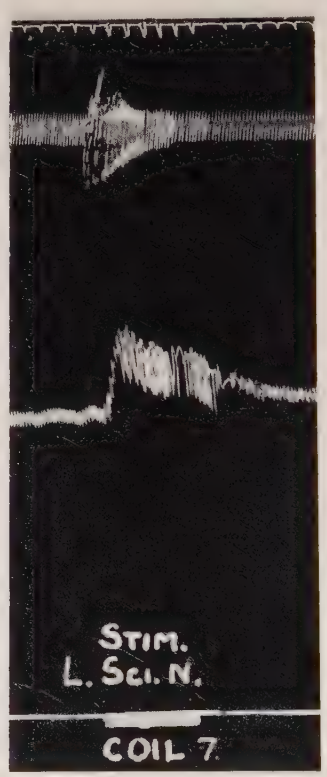


FIG. 61 FIG. 62

FIG. 61. Blood-pressure tracings showing the production of extrasystoles by sciatic stimulation, with the stellate ganglia intact but with the adrenal glands removed. The respiration curve is below the time marker which is indicating five-second intervals.

FIG. 62. Blood-pressure tracing showing the production of extrasystoles by sciatic stimulation, the stellate ganglia being removed and the adrenal glands intact. The respiration and time marker are the same as in Fig. 61.

remains effective, provided the nerve stimulated has its entrance into the cord above the level of the transection. In the latter case, the only route intact is the nerve-pathway to the heart, via the anterior roots

in the second, third and fourth thoracic anterior roots. These observations carry to a higher level in the nervous system the effects of sensory stimulation as recorded by Levy.

The stimulation of the sciatic nerve did not call forth extrasystoles in animals which had exhibited extrasystoles under chloroform, and whose hypothalamic region had been transected later, thus abolishing the abnormal rhythm. In these animals the adrenal glands were intact, as well as the nerve-connections to the heart, but the stimulation of the sciatic nerve produced a small rise in blood-pressure. There are, therefore, centres below the level of the hypothalamus which can give rise to pressor effects. Cannon (21) has shown that the reflex secretion of adrenalin can still be called forth when the tegmentum of the lower midbrain is intact. Although the authors have not been able to induce irregularities by sciatic stimulation in animals with wounds in the hypothalamus, the possibility of producing extrasystoles still remains.

When the level of section between the anterior edge of the superior colliculus and the optic chiasm is examined, it is seen that the ventral nuclei of the thalami are intact, but all of the globus pallidus of the corpus striatum is removed. Such a section does not abolish extrasystoles. When the thalamus is removed by a section parallel to the middle line, the stimulation of the sciatic nerve is ineffective. It may be concluded that the normal sensory side of the arc for the reflex secretion of adrenalin and for cardiac acceleration produced by sensory stimulation, reaches as high as the thalamus and probably ends there. Since the corpus striatum is removed by the section described above, it would seem probable that the connections of the thalamus to the hypothalamus are direct and do not pass via the striatum.

In the present experiments, therefore, sensory stimulation is effective as long as the thalamus and hypothalamus are intact, and either the anterior roots of the second, third and fourth thoracic nerves or the adrenal glands have been left untouched. The authors consider, then, that although the lower centres mentioned above may remain active after hypothalamic section, the full effect of sensory stimulation on adrenalin secretion and cardiac acceleration is not obtained after the projection pathways from the hypothalamus have been severed.

THE EFFECTS OF SECTION OF THE VAGUS NERVE

When extrasystoles have been produced in an animal by the inhalation of chloroform, and the vagi are sectioned, the extrasystoles still

persist. The blood-pressure tends to rise and the rate of the heart will increase. This increased work on the part of the heart may accentuate the arrhythmia and drive the heart into ventricular fibrillation. This is due evidently to the release of the organ from the controlling influence of the vagus nerve. The extrasystolic arrhythmia, then, is not affected by vagal section except insofar as it may become more

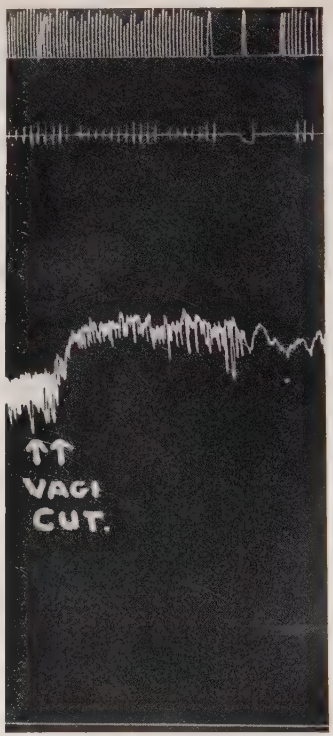


FIG. 63. Blood-pressure tracing showing that section of the vagi does not abolish an extrasystolic arrhythmia induced by chloroform anesthesia. The respiration curve is above. Time marker indicates five-second intervals.

marked or, if not present, it may be induced by the act of section (Figs. 63 and 64).

THE EFFECTS OF VAGAL STIMULATION

In considering the effects of vagal stimulation, there are two distinct results to be considered. Strong stimulation of the central end of the

vagus nerve (when sectioned) has been shown by Houssay and Mollinelli (32) to cause a reflex secretion of adrenalin. This is not the only effect, for the authors have shown that when the adrenal glands are removed, central stimulation will still give rise to extrasystoles if not previously present, when the animal is under chloroform. In this way, there seems to be no difference between the effects of vagus (central) stimulation and stimulation of the sciatic nerve or of any other sensory nerve, provided both vagi are sectioned. When one vagus is intact and the central end of the other is stimulated, a slowing of the heart occurs, along with an abolition of the extrasystoles (Fig. 65).

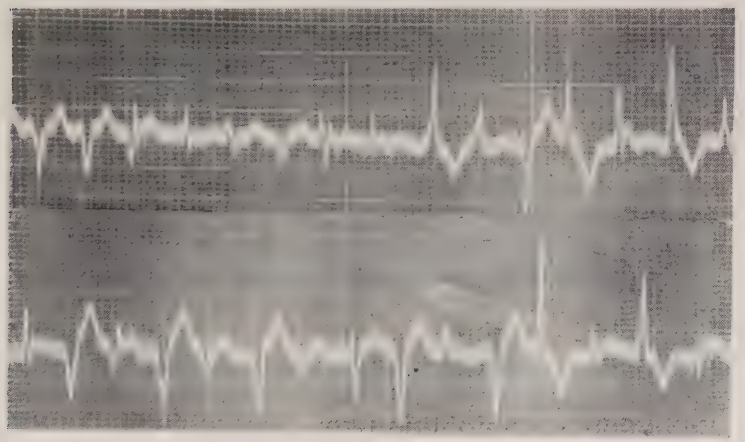
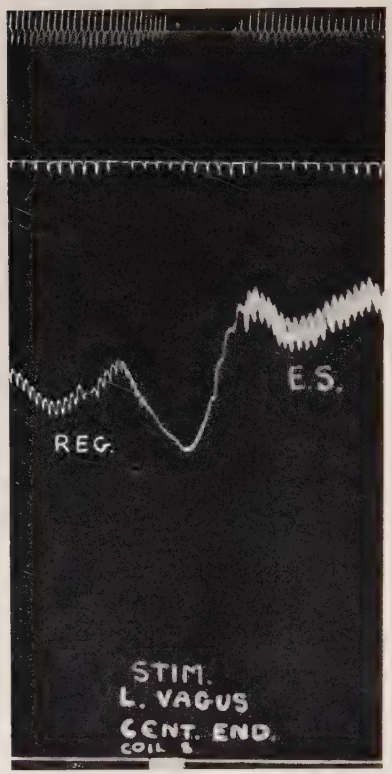


FIG. 64. Electrocardiographic tracings taken during the experiment cited in Fig. 63: *a*, extrasystolic arrhythmia under chloroform anesthesia; *b*, the persistence of this condition after section of both vagi.

The stimulation of the peripheral end of the vagus nerve produces an entirely different effect from central stimulation. The heart-rate immediately slows, with a complete disappearance of the extrasystoles. On cessation of the stimulus, the irregularities reappear and continue (Figs. 66 and 67). They can be obliterated again by restimulation. The explanation of this effect seems to be that the slowing of the heart-rate and the fall in blood-pressure diminish the work of the heart per minute, and so tend to fulfil the opposite conditions required for the production of ectopic beats.

THE EFFECTS OF VARIOUS DRUGS ON CARDIAC IRREGULARITIES

Nicotine. The authors have dealt with this drug in their review of the work of Goodman Levy. They have shown that in small doses or in the first stage of the action of the larger doses, the extrasystolic arrhythmia tends to be accentuated. The painting of the stellate



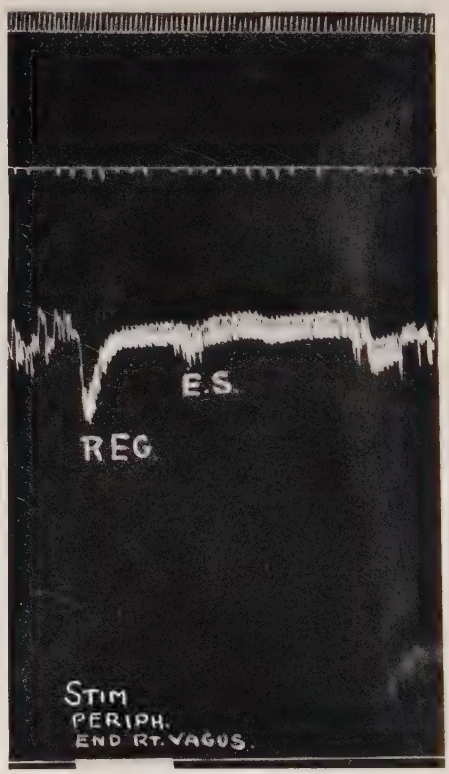


Fig. 65 Fig. 66

Fig. 65. The effect of stimulation of the central end of the left vagus nerve, the right nerve being intact. After a preliminary fall in blood-pressure the arrhythmia appears. This observation was confirmed by the electrocardiograph. The respiration and time marker are the same as in Fig. 63.

Fig. 66. Stimulation of the peripheral end of the right vagus, showing the abolition of the extrasystolic arrhythmia which returned after the cessation of the stimulation. The left vagus was intact. The respiration and time marker are the same as in Fig. 63.

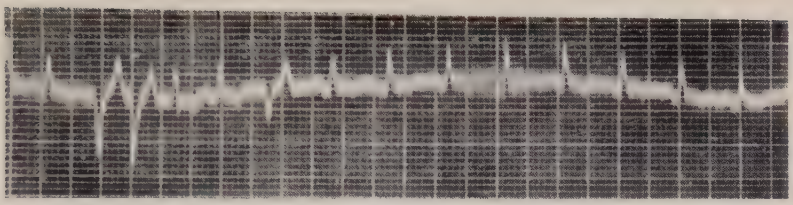


FIG. 67. Electrocardiographic tracing taken at the time of stimulation of the vagus cited in Fig. 66 This tracing shows the cessation of the extrasystoles and the appearance of regular rhythm.

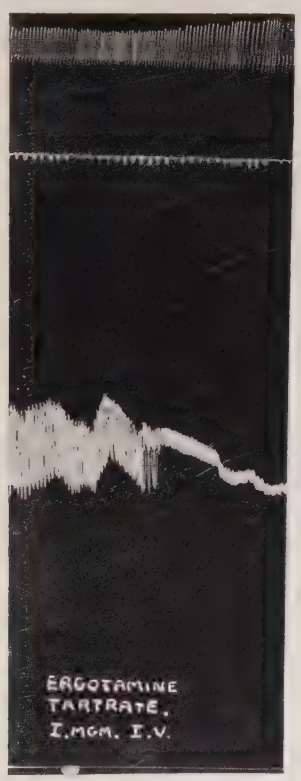


FIG. 68. Blood-pressure tracing showing the abolition of the extrasystoles produced by chloroform anesthesia, by the injection intravenously of 1 mg. of ergotamine tartrate.

ganglia or the injection of the drug into the circulation causes a disappearance of the extrasystoles. The observations of Levy as to the effects of this drug have, therefore, been confirmed by the present study.

Ergotamine. A few experiments were made as to the effects of ergotamine on the irregularities of the heart, under chloroform. When 1 mg. is injected intravenously into an animal, the heart slows,

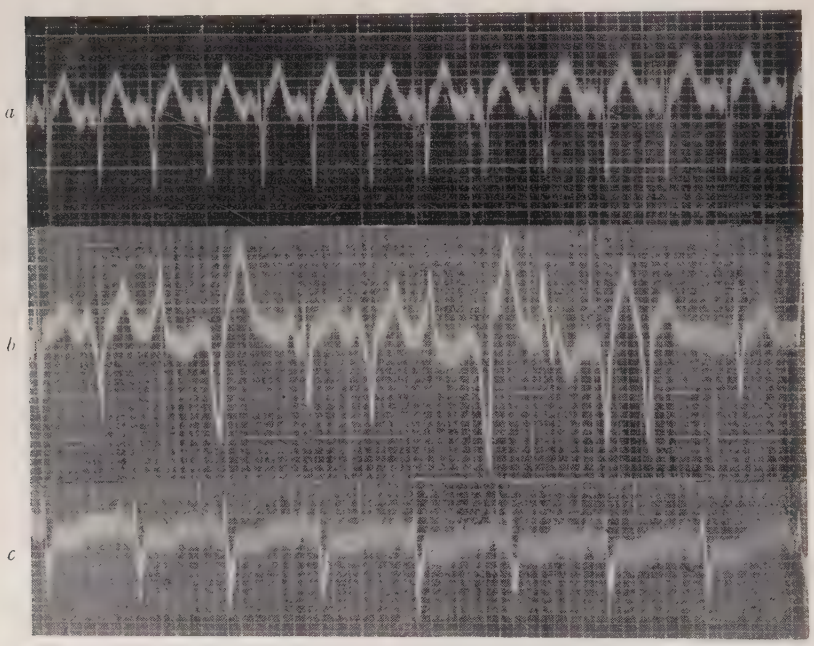


FIG. 69. Electrocardiographic tracings of the experiment cited in Fig. 68: *a*, regular rhythm; *b*, extrasystolic arrhythmia under chloroform anesthesia; *c*, the return to regular rhythm after the injection of ergotamine. The vagi are intact and there is marked slowing of the heart in tracing *c*.

the extrasystoles disappear, and the blood-pressure tends to fall slightly. With the anesthetic unchanged, the irregularities tend to reappear again after about thirty minutes. When 1 mg. is injected, the normal effect of adrenalin on the blood-pressure cannot be produced. Thus the drug in this dosage completely paralyzes the whole of the sympathetic nerve-endings. The pressor effect gradually reappears as time goes on (Figs. 68 and 69).

Adrenalin. The authors can substantiate all the findings of Levy (41–43) as to the effects of this drug. It increases the rate of the heart, as well as the force of the beat. Under chloroform, as soon as the cardiac effect has appeared after injection, extrasystoles can be seen electrocardiographically but not necessarily on the blood-pressure curve. Without anesthesia and with the animal decerebrated for some hours, the injection of 5 mg. of the drug will give rise to well-marked extrasystoles. This effect has been discussed above (pp. 262–264).

Caffeine. When caffeine is injected into an animal under di-allyl-barbituric acid, in an amount equal to about 35 to 45 mg. per kilo of body-weight, the heart shows extrasystoles. In a decerebrate animal, five hours without an anesthetic, the injection of 2 cc. of caffeine in a 1 per cent solution produced a few extrasystoles, but the effect was transitory. When chloroform is applied, the amount of caffeine required is decreased. The section of all the nerve-connections to the heart and the removal of the adrenal glands have no effect whatever on the arrhythmia. From this it is concluded that the effect of caffeine is actually on the heart itself, either on the myocardium or on the sympathetic nerve-endings within the organ. The production of extrasystoles in normal human hearts by the use of caffeine, is well known.

Ether anesthesia. The authors have demonstrated that ether anesthesia will spontaneously give rise to an extrasystolic arrhythmia. They have observed this phenomenon in two experiments. They feel, however, that it may occur much more frequently, since they did not take records in every animal anesthetized by ether.

Di-allyl-barbituric acid anesthesia. In one animal, extrasystoles were observed under di-allyl-barbituric acid anesthesia. The irregularity appeared spontaneously and persisted for one hour.

AN ANALYSIS OF THE ELECTROCARDIOGRAPHIC TRACINGS

The Effect of Chloroform on the Sino-Auricular Node

The rate of discharge from this pacemaker in the normal unanesthetized animal has not been determined by the present investigators. They used instead, as a control, the rate of the node immediately after full anesthesia had been obtained, but with the corneal reflexes still present. At this stage of anesthesia, the rate of the heart was on an average between 180–210 per minute. Animals have been seen with a heart-rate of 120 without any sign of heart-block and, again,

animals with a heart-rate of 300, without any signs of struggling. The latter figure was often obtained under ether anesthesia.

Using the standard concentration of anesthesia in 95 per cent oxygen and 5 per cent carbon-dioxide, it was found that the normal rate of discharge dropped only slightly during the course of the anesthesia. When the figure is higher than 210, the rate may drop to 180 after some hours. A slow heart-rate frequently rises to within the limits of normal, as outlined above. With the concentrations of chloroform greater than 3 per cent in the above gas mixture, the rate may drop steadily to 120 and in many animals varying degrees of heart-block may develop. Unless the anesthetic is removed or the concentration of it lowered, complete block ensues.

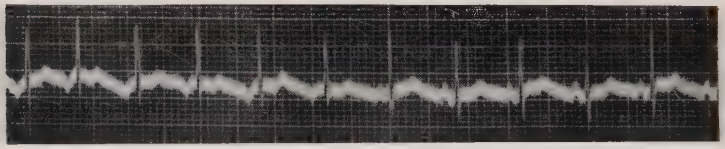


Fig. 70. Electrocardiographic tracing showing the changing pacemaker after the heart had been removed from sympathetic control. The vagi were intact.

The Effect of Sympathetic Stimulation on the Sino-Auricular Node

The rate of discharge from the sino-auricular node rises considerably on sympathetic stimulation. In one animal, whose stellate ganglia were stimulated during chloroform anesthesia, the rate rose from 210 to 280 per minute. Stimulation of the proper region of the hypothalamus also increases the rate of discharge. In one experiment, the number of P-waves rose from 210 to 270 per minute. Any rise in rate under these experimental conditions was regarded as evidence of some sympathetic stimulation.

The Effect of Extirpation of the Sympathetic Pathways on the Sino-Auricular Node

When any part of the sympathetic pathways to the heart is severed, the rate of discharge from the sinus-node falls. In one experiment where the hypothalamus was transected, the rate fell from 240 to 180 per minute; in another the fall in rate was from 180 to 120 per minute. In still another animal, there was no change in rate three minutes after the brain-section, but later the rate fell to 210 per minute.

TABLE IV

Changes in P-R Interval, Auricular Rate, and Rhythm of the Heart during Stimulation and Extirpation of Different Parts of the Sympathetic Nervous System under Chloroform Anesthesia

Cat No.		P-R Interval		Auricular Rate		Irregularities	
		Before Stimulation	After Stimulation	Before Stimulation	After Stimulation	Before Stimulation	After Stimulation
A. Stimulation of the Hypothalamus							
		seconds	*seconds*	*per minute*	*per minute*		
70.N.S.	Control	0.08		150		Regular	
70.N.S.	Stimulation of left hypothalamus	0.085	0.07	120	180	Regular	Extrasystoles
70.N.S.	Stimulation of left hypothalamus		0.07		210	Regular	Extrasystoles
70.N.S.	Stimulation of left hypothalamus	0.08	0.06	120	180	Regular	Extrasystoles
70.N.S.	Stimulation of an anterodorsal region of the left hypothalamus	0.08	0.08	150	150	Regular	Regular
70.N.S.	Stimulation of cerebral cortex	0.08	0.08	150	150	Regular	Regular
70.N.S.	Stimulation of corpus callosum	0.10	0.10	120	120	Regular	Regular
71.N.S.	Control	0.08		150		Regular	
71.N.S.	Stimulation of right hypothalamus		0.06		210	Regular	Extrasystoles
71.N.S.	Stimulation of right hypothalamus		0.06		180	Regular	Extrasystoles

Cat No.	P-R Interval		Auricular Rate		Irregularities	
	Before Section	After Section	Before Section	After Section	Before Section	After Section
B. Section of the Hypothalamus						
	seconds	*seconds*	*per minute*	*per minute*		
83.O.S.	0.06	0.08	240	210	Extrasystoles	Regular
34.O.S.	0.06	0.07	240	180	Extrasystoles	Regular
42.O.S.	0.06	0.07	180	120	Extrasystoles	Regular
C. Section of Anterior Roots of Second, Third and Fourth Thoracic Nerves on Both Sides						
38.O.S.	0.06	0.08	300	210	Extrasystoles	Regular
85.O.S.	0.04	0.06	270	240	Extrasystoles	Regular

Section of the anterior roots of the second, third and fourth nerves also caused a fall in rate. In one experiment, the fall was from 300 to 210, and in another from 270 to 240.

When the sympathetic influences to the heart are removed by any operative procedure, the vagus nerve being intact, the node may be depressed to such an extent that it fails to discharge any impulses, and another region in the auricle takes over control. This is illustrated particularly well in one experiment (Fig. 70) where the P-wave is seen to be inverted for a time and then to return gradually to the normal upright form. The depression is apparently due to the uncontrolled influence of the vagus nerve.

The Effect of Chloroform on the Auricle

Only in one experiment out of a total of 175 have the authors observed auricular extrasystoles under chloroform anesthesia. In another experiment, they observed a few auricular extrasystoles under ether anesthesia. These animals were the only two which showed ectopic beats arising in the auricle.

The Effect of Chloroform on the Auriculo-Ventricular Conduction Time

The average conduction time in these experiments was 0.08 second. This was a remarkably constant feature in all the control tracings. A lengthening of the conduction time was found to take place when the animal was under the influence of chloroform in amounts of 3 per cent, or greater. When the anesthetic was prolonged for some hours, there was a tendency for the conduction time to lengthen. This was found to be an almost infallible sign that heart-block was imminent. The removal of the anesthetic or diminishing its concentration obviated this difficulty.

The Effect of Sympathetic Stimulation on the Auriculo-Ventricular Conduction Time

It has been shown by Andrus and Martin (2), in dogs, that the transmission rate of the impulse from the auricle to the ventricle is considerably increased by the injection of adrenalin. The effect takes place within a minute from the time of injection and lasts about five minutes. These observers used doses of adrenalin varying in amount from 0.25 cc. to 1.00 cc. of adrenalin in a concentration of 1:50,000.

In these experiments they excluded the effect of the vagus nerve by the preliminary injection of atropine.

Stimulation of the hypothalamus diminishes the conduction time from 0.08 to 0.07 or 0.06 second. This is accompanied, as has been shown before, by an acceleration of the heart. Similar effects are seen when the stellate ganglia are stimulated, or during the stimulation phase after section of the anterior roots of the thoracic nerves.

Consequently, in the shortening of conduction time, there is a valuable indication of excitation of the sympathetic nervous system.

The Effects of Extirpation or Paralysis of the Sympathetic Pathways on the Auriculo-Ventricular Conduction Time

Andrus and Martin (2), in the paper referred to above, made some very interesting observations on the effect of the injection of ergotamine on the transmission rate and conduction time between the auricles and ventricles. With the vagi intact, the injection of 0.25 mg. of ergotamine increased the conduction time from 0.07 to 0.08 second. The further injection of the same dose of the drug caused an increase from 0.08 to 0.09 second. After the first injection, the rate of the heart was diminished from 222 per minute to 136, after four minutes. After the second injection there was no further fall in rate.

Similar effects have been observed by the authors on the injection of ergotamine under chloroform anesthesia. One animal showed a slowing from 0.04 to 0.06 second, after 1 mg. of ergotamine. These effects are identical with those observed in the extirpation of the sympathetic connections of the heart. In section of the anterior roots of the upper thoracic nerves (Table IV), the conduction time lengthened from 0.06 to 0.08 second in one animal, and from 0.04 to 0.06 second in another. Section of the hypothalamus produced similar effects.

Thus a lengthening of conduction time is, apart from the disappearance of extrasystoles, a valuable check on the efficacy of a section of the sympathetic pathways.

The Effect of Chloroform on the Ventricular Complex

Under light anesthesia with concentrations of chloroform of 2 per cent, or less, in the oxygen-carbon-dioxide gas mixture, the QRS complex does not change appreciably after two or three hours of this depth of anesthesia. With higher concentrations of chloroform or with prolonged anesthesia induced by a 2 per cent vapor concentration in air,

the QRS tends to become wider and the amplitude of the deflection smaller. As time goes on, the QRS changes into a diphasic and, still later, into a negative form.

Sympathetic stimulation or the injection of adrenalin does not affect the form, amplitude, or width of the complex of the normal QRS when normal beats appear interspersed with an extrasystolic arrhythmia.

The Abnormal Ventricular Complexes (Ventricular Ectopic Beats)

The abnormal beats which disturb the regular rhythm after a period of light anesthesia or after the injection of adrenalin into a non-anesthetized animal, are of varying forms. The ectopic beats may arise either in the right or in the left ventricle. Another abnormal type has been observed which has been called by Lewis the "transitional type." His description of this type is as follows. "When a stimulus enters the ventricle in very late diastole, the whole ventricle does not respond to it, some parts of the chamber being simultaneously excited by the natural impulse descending from the auricle. In shape it is intermediate between the natural complex and that resulting purely from the artificial stimulus, the P-R interval being slightly shortened." (Lewis (45), p. 217.)

These observations of Lewis's on the stimulation of different areas of the ventral wall of the dog's heart, show that the varying form of the resultant ectopic beat depends upon two factors: (*a*) the distance of the point of stimulation from the Purkinje tissue, i.e. the thickness of the ventricular wall at the point of stimulation; and (*b*) the particular part of this system (right or left arborizations) which are first excited. The closer the points of stimulation, the more similar were the forms of the ectopic beats. On the basis of this work, the observations would go to show that the point of origin of the excitatory process for the ectopic beats was constantly changing. The stimulation of the sympathetic nerves produces extrasystoles which may arise in any part of the ventricular wall or in the Purkinje system.

On the administration of chloroform in low concentrations the authors have frequently observed that the abnormal beats appear first as single complexes; then isolated in extrasystoles alternating with normal beats; later in paroxysmal extrasystolic tachycardial groups arising either in the right or left ventricles, or in both, or alternating rapidly between these chambers.

When these beats occur in bigeminal form, i.e. a normal beat followed by a premature ventricular beat, they are very often accurately coupled with the preceding normal cycle. When, however, these premature ventricular beats appear in groups or in tachycardial forms, the rhythm is totally and completely irregular. If an alternation between the right and left ventricular forms occurs, the time interval from cycle to cycle alters and is quite irregular. These features are applicable to the arrhythmias induced by low chloroform vapors as well as to those occurring under sympathetic stimulation, either by direct stimulation or after adrenalin injection into the blood-stream.

The form of the T-deflection does not depend upon the integrity of the sympathetic nervous system. In animals under the standard of chloroform anesthesia used, no change in this wave was observed. When the depth of anesthesia is increased, or the oxygen saturation of the blood falls, the T-wave tends to become iso-electric or negative. It is probable that changes of this kind in the T-wave are caused by anoxemic factors rather than by any other specific myocardial change.

Summary of the Electrocardiographic Findings

1. The average nodal rate of discharge in the fully anesthetized animal under chloroform anesthesia was between 180–210 per minute.

2. The length of anesthesia alone caused no appreciable fall in the heart-rate, if all other factors were kept constant and the heart was supplied with well-oxygenated blood.

3. Deep degrees of anesthesia readily induced heart-block, especially if the oxygenation of the blood was defective.

4. Sympathetic stimulation caused a rise in the rate of discharge of the sino-auricular node.

5. When the vagus nerve was intact, sympathetic extirpation caused a fall in the heart-rate.

6. With the vagus severed, the same effect was produced, but in a lesser degree.

7. After sympathetic extirpation, with the vagus intact, the sino-auricular node may be depressed sufficiently to permit another region of the heart to take over control.

8. Auricular extrasystoles were not commonly observed under chloroform anesthesia.

9. The effect of chloroform anesthesia on the conduction time between the auricles and the ventricles was not appreciable, provided that full oxygen-saturation of the blood was maintained.

10. Sympathetic stimulation diminished the A-V conduction time.

11. Sympathetic extirpation had the reverse effect.

12. The normal ventricular complex was not appreciably affected by anesthesia.

13. Sympathetic stimulation or extirpation had little or no effect on the QRS complex.

14. The abnormal ventricular complexes induced by chloroform anesthesia, or by the injection of adrenalin, or by the stimulation of the sympathetic nerves to the heart, were of varying forms, arising from different points within the ventricles.

COMMENT

The experiments cited above leave no doubt that section of the sympathetic pathways to the heart abolishes the extrasystolic arrhythmia due to chloroform anesthesia. Furthermore, the electrocardiographic records demonstrate that this abolition is caused by the removal of a true sympathetic effect; that, consequently, the heart-rate falls and the P-R interval lengthens.

Stimulation of the sympathetic pathways to the heart, or stimulation of sensory nerves reflexly, produces or accentuates the arrhythmia. The heart-rate rises and the P-R interval shortens.

Consequently, this arrhythmia can be used as an index of the integrity of the normal sympathetic pathways to the heart; and by this means, it has been possible to demonstrate the existence of a higher centre for sympathetic activity in the hypothalamus.

Part Two

The Higher Connections of the Sympathetic Nervous System as Studied by Experimental Lesions of the Hypothalamus[4]

I. Introduction
II. The Effects of Lesions of the Hypothalamus
III. The Site of the Experimental Lesions
IV. Comment
V. Summary

INTRODUCTION

IN 1928, Greving (28) summarized the literature on the structure of the hypothalamus and added the results of a series of investigations of his own. Although he has described the distribution of the cell-masses and the fiber tracts of the hypothalamus, there are still large gaps in the knowledge of the exact termination of the long projection tracts. There has been no direct anatomical proof of the connection between the hypothalamus and the lower parts of the central nervous system. In the present paper, the authors will attempt to show the degenerations which result after lesions in the hypothalamus.

Greving has divided the cell-masses of the hypothalamus into the following groups:

1. Substantia grisea centralis
2. Nucleus supra-opticus
3. Nucleus paraventricularis (Malone)
4. Nucleus tuberis
5. Nucleus mammilo-infundibularis (Malone)
6. Nucleus pallido-infundibularis
7. Nucleus interfornicatus (Greving)
8. Nucleus intercalatus (Malone)
9. Nucleus subthalamicus (Luys)
10. Substantia reticularis hypothalami
11. Nucleus reuniens
12. Nucleus paramedianus

It has been shown in Part One (p. 272) that a complete transection of the brain passing from the anterior edge of the superior colliculus to

[4] The authors wish to thank the Trustees of the Cooper Fund of McGill University for grants in aid of this research.

the posterior border of the optic chiasm is not effective in abolishing extrasystoles. When the brain posterior to such a section is examined, it is seen that the following cell-masses are not to be found in the remaining hypothalamus: the nucleus supra-opticus, nucleus paramedianus, and nucleus reuniens. It has also been shown that a complete transection is not necessary to produce the abolition of extrasystoles, but that a stab-wound is effective. Such a wound should extend 2 mm. on each side of the middle line in the plane drawn from the anterior edge of the superior colliculus to the anterior edge of the mammillary body. Consequently it is probable that there is no involvement of the nuclei which lie farther than 2 or 3 mm. from the middle line. Such nuclei would include the nucleus subthalamicus of Luys, nucleus intercalatus, nucleus interfornicatus, and nucleus pallido-infundibularis. The examination of the region surrounding the experimental lesions shows, however, that no degeneration has been traced to these nuclei, and they are apparently normal in this series. The possibility is not precluded that some of their connections have been disturbed. There is no doubt that almost all of the following nuclear masses or their projection pathways were involved in the lesions produced: substantia grisea centralis, nucleus paraventricularis, nucleus mammillo-infundibularis, and substantia reticularis hypothalami. In one animal, the nucleus tuberis was considerably damaged; and in the others the projection fibers from this nucleus were probably severed.

It is possible to deduce from Greving's work (28) that the hypothalamus can be divided into two parts which may differ considerably in function: (*a*) the supra-optic infundibular complex, and (*b*) the tuber-paraventricular complex. Fulton, in some unpublished work, apparently demonstrates that the anterior or supra-optic complex differs markedly from the posterior or paraventricular portion. He has shown that lesions in the prechiasmatic hypothalamus produce profound changes in the behavior of the animal. These changes partake of a definite increase in the "wildness" of the animal. Hissing, growling and attempted biting were seen within forty-eight hours after operation, and persisted. In the authors' animals, with lesions posterior to the level of the lesion used by Fulton, no such changes were observed. On the contrary, a completely opposite effect was noted. Animals which had been inclined to be ferocious or wild, became very docile and could be fed easily by hand. This change lasted until the animal was killed after four or five weeks.

THE EFFECTS OF LESIONS OF THE HYPOTHALAMUS

Experimental Methods

Animals. Cats were used in all the recovery experiments. In all, sixteen animals were operated upon and allowed to recover. In the early group of eight, bilateral lesions were attempted. Unilateral lesions were produced in the later animals.

The animals which were given bilateral lesions died within ten days. The causes of death may be subdivided as follows:

Meningitis and encephalitis.....3 (within three days)
Meningitis and encephalitis.....1 (after eight days)
Pneumonia.....2
Unknown.....2

The three animals dying within three days of operation, had extensive meningitis due no doubt to faulty technique. The animal dying after eight days, had been allowed to recover; though no attempt had been made to repair the palate. The animal was examined on the sixth day. Under an anesthetic the nasopharynx was washed out and some sloughs removed. There is little doubt that the mere handling of the wound in the roof of the pharynx allowed organisms to enter non-infected areas. One of the animals dying of pneumonia had been given 50 cc. of milk immediately after operation. This was vomited some hours later and some of the fluid was aspirated into the lungs. The other animal also had an aspiration pneumonia. In this case the palate was not repaired; and whenever the animal attempted to drink milk, it coughed violently. The two animals dying from "unknown" causes, had no trace of pneumonia changes in the lungs and no sign of infection of the meninges. The wound in the sphenoid was granulating well and was not very badly infected. Each animal lost over 500 gm. before death. One living to nine days, lost 550 gm.; and another to ten days, lost 600 gm.

In the later series, attempts were made to produce unilateral lesions. Eight animals were used, but only two of these survived for a period greater than twenty-eight days. The others died at various times and from various causes:

Meningitis and encephalitis.....2 (within three days)
Pneumonia.....1 (within forty-eight hours)
Unknown causes.....3 (after ten days)

In all, seven animals survived long enough to permit making observations on their nervous system. One animal was not examined, as it had been dead for over twelve hours before being autopsied. Of the six animals, two were examined by the Marchi method and the remaining four by the Alzheimer-Mann technique.

Anesthesia. During the early series of survival experiments di-allyl-barbituric acid was used as an anesthetic. With this drug it was possible to obtain complete anesthesia for a period of thirty-six hours with doses of 0.5 to 0.6 cc. per kilo of body-weight. The drug was used in the form of the proprietary preparation "dial." It was injected into the peritoneal cavity.

It was hoped to gain many advantages through the use of this drug. It was not

found necessary to give supplementary doses after some time as is the case with amytal or chloralose, nor was it necessary to expose a vein for the purpose of injection. It was thought that the length of anesthesia would prevent any unnecessary movement during the first twenty-four hours after the operation, and that the animal could be fed without any struggling, or the danger of hemorrhage.

These advantages, however, were more apparent than real. It was found that as a rule it was better to have the animal recover quickly from the effects of the anesthetic and to risk the possibility of hemorrhage from the site of the operation. Consequently, either 2 per cent of chloroform was used in the gas mixture, or ether on a mask. Recovery from the anesthetic took place within a few hours and the animal remained quiet for the first three days.

Operative procedure. The method of approach described by McLean (47) was employed. After the buccal cavity had been washed out with sterile saline solution, the whole region was painted with 1 per cent mercurochrome in watery solution. The soft palate was split in the middle line from about 2 mm. posterior to the edge of the hard palate. The incision was continued backwards and stopped so as to leave about 1 cm. of the soft palate intact at the posterior end. The edges were retracted either with small mastoid retractors or by means of sutures inserted through the soft palate near the cut edge. The edges of the wound were swabbed with mercurochrome and the nasal cavity washed out in the same manner as the mouth. Sterilizaton was attempted by using mercurochrome.

The mucoperiosteum on the basisphenoid was split in the middle line and retracted as it was being elevated from the bone. With the posterior edge of the pterygoid lamina as a guide, a dental drill was used to bore away a small hole about 5 mm. wide in the middle line and with the posterior edge of the hole in line with the pterygoid lamina. When the dura and the underlying pituitary gland were seen through a thin bony plate, the most inferior part of the pituitary fossa was determined. At this inferior limit the bone was drilled through in the middle line and with care the dura was exposed for about 4 or 5 mm. in the transverse plane. Bleeding was controlled by muscle compresses. The dura was next incised in a longitudinal plane with a fine cataract knife. Any degree of traction on this dura led to bleeding. The pituitary gland bulged only a little into the wound, when the incision into the dura had been kept small (2 or 3 mm.). The risk of meningitis was lessened materially if the gland could be retained within its dural coverings. The knife (described in Part One, p. 273) was then inserted through the gland-substance in such a manner as to strike the posterior and upper edge of the pituitary fossa. On reaching the roof of the fossa the knife was allowed to penetrate the dura just in front of this posterior edge and to travel into the brain substance so that the total depth of the incision was 1 cm. from the entrance into the dura covering the floor of the fossa. In this way it was possible to produce lesions which were in the plane necessary to abolish extrasystoles. Controls were made in the acute experiments and it was found that such a stab-wound as that described above and measuring only 2 mm. laterally from the middle line, would abolish extrasystoles in a cat under chloroform.

The wound in the palate should be sewed up carefully. Although McLean recommended two layers of sutures in his animals, the authors found that such duplication was unnecessary if the apposition of the suture line was accurate. The

line must be watertight and the sutures should be of fine linen or silk. Before being removed from the table, 50 cc. of water or milk should be placed in the stomach by a stomach tube. The animal should then be placed in a heated cage, with hot water bottles, and on a wire floor so that the urine can be collected.

Histological Technique

Two methods were used in investigating the degenerations following lesions in the hypothalamus: (*a*) the Marchi method, and (*b*) the Alzheimer-Mann method. The latter technique is valuable, since changes in the degenerating axone can be detected at a very early stage (five days). The normal axone stains blue and the degenerating one, pink. As the stain is specifically for axone degeneration and not for myelin degeneration, it gives very accurate pictures of the changes in medullated or non-medullated fibers.

Postoperative Observations

Sleep. It was found as a constant feature that the animals were very lethargic and drowsy for two or three days after the operation. The lethargy persisted during the whole of the subsequent life of the animals (thirty-one days maximum). The day after operation they were very hard to rouse and after being awakened invariably went off to sleep again.

Behavior. It has been noted above that the animals became very quiet and docile after operation. In every case the affected animals sought the warmest part of the animal-room when released from the cages for exercise. They crept close to radiators and huddled themselves against the pipes. Even in weather below zero pilo-erection was never observed on the side of the lesion, although the unaffected side showed the erection normally. In complete bilateral lesions, pilo-erection was always absent.

Temperature. No continuous record of temperature was kept in the case of each animal. It was noted, however, that on the occasions on which a rectal temperature was taken, it was about 36.5°C. or 37°C., when normal animals showed a temperature of 38°C.

Glycosuria. Every animal operated upon had a definite glycosuria within twenty-four hours of operation. The amount observed in the urine at the end of twenty-four hours varied from 2.25 per cent to 1.14 per cent. At the end of forty-eight hours, the amount was almost the same (2.30 per cent to 1.5 per cent). During the first week the glucose gradually fell and reached a level varying from 0.4 per cent to 0.7 per cent. After this time the fall continued. In two animals which survived for over four weeks, the glucose was absent in measurable quantities after about sixteen days. All traces had vanished by the twenty-fourth day. These animals had unilateral lesions. In one animal (Cat 5.R.) the blood-sugar was 0.118 per cent one hour after operation, 0.129 per cent two hours afterwards, and 0.138 per cent six hours afterwards. At the end of twenty-four hours it had risen to 0.492 per cent. Forty-eight hours after operation it had fallen to 0.210 per cent. The corresponding glycosuria at the end of forty-eight hours was 2.25 per cent.

Albuminuria. Each animal showed a marked amount of albumen in the urine during the first four or five days after operation. In one animal (Cat 38) the blood-

urea was 0.372 gm. per liter and the urea-nitrogen 17.36 mm. per 100 cc., twenty-four hours after operation.

The albuminuria was most marked in those animals anesthetized by di-allyl-barbituric acid.

Polyuria. No continuous records of the urine output were kept. The animals drank very much more than normally, consuming as much as 500 cc. of milk per day during the first week. After this time the amount consumed was very much less.

Pupillary changes. Immediately after an effective section had been made, the pupil was found to be contracted. As the effect of the anesthetic disappeared, the contraction became more and more marked until the pupil was slit-like. The pupil

FIG. 71. A coronal section through the anterior part of the corpora mammillaria, showing the anterior end of a unilateral lesion in the lateral wall of the third ventricle. Note the decussating fibers below the ventricle, which have degenerated.

in this state did not react to light. After two or three days the contraction became less marked. As it did so, the reaction to light reappeared, sluggish at first, but eventually it became normal.

THE SITE OF THE EXPERIMENTAL LESIONS

It has already been pointed out (pp. 272, 295, 296) that a lesion which is effective in abolishing extrasystoles, lies in the colliculo-mammillary plane. In all the recovery experiments the lesions, whether unilateral or bilateral, were planned to lie in this plane. In every operation the

lesion entered either through, or in front of, the mammillary bodies. In depth it extended as far as the lateral limit of the periventricular gray matter and about 1 to 1.5 mm. in an anteroposterior direction. Figures 71 and 72 show the lesion in one of the survival experiments.

When an attempt is made to correlate the site of experimental lesions in the hypothalamus, one is faced with some difficulty in terminology. At least three nomenclatures for cell-masses have been proposed (Winkler and Potter (56), Gurdjian (29), and Greving (28)).

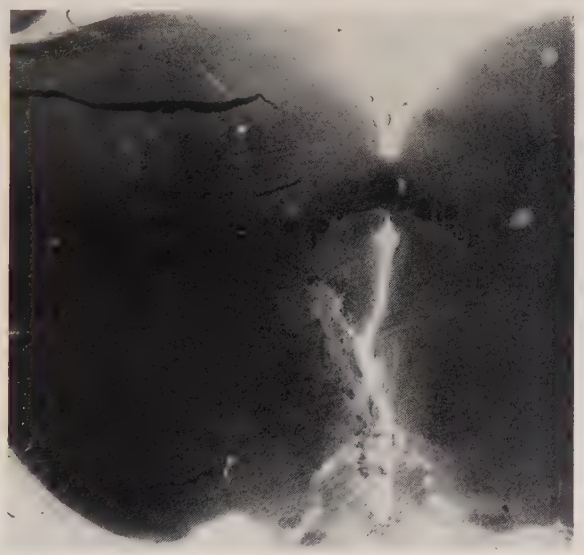


FIG. 72. A coronal section through the anterior part of the interpeduncular space, showing the point of entrance of the knife in producing a unilateral lesion.

Gurdjian working on the brain of the albino rat, has described the hypothalamic nuclei and their connections in this animal in such a way that there is little difficulty in applying the explanation to the brain of the cat. Winkler and Potter described the cat's brain, but their study of the hypothalamus was not complete. Greving, using human material, described hypothalamic nuclei under different names from those adopted by Gurdjian. In general, from a study of toluidine-blue preparations, Gurdjian's description fits fairly closely the distribution of the nuclear masses in the cat.

The Nuclear Masses

It has previously been pointed out (p. 296) that the hypothalamic nuclei are divided probably into two groups—a supra-optico-hypophysia group and a posterior hypothalamic group. Greving emphasizes the intimate connection of the supra-optic group with the hypophysis. Although there also exists a connection between the hypophysis and the posterior hypothalamic group, it is not so extensive as is the former relationship. Gurdjian points out that the cell-masses associated with the periventricular fiber-tracts lie in the more posterior region of the hypothalamus. Such a condition would seem to be present in the cat. Stimulation, to be effective in the production of extrasystoles, must be carried out in the posterior hypothalamic region. Again, the major part of the supra-optic group of nuclei are cut off when a section is made from the anterior edge of the superior colliculus to the caudal edge of the optic chiasm. Such a section does not abolish extrasystoles, as has already been pointed out.

When the hypothalamic nuclei are examined posterior to this line of section, the cell-masses can be subdivided into the following nuclei:

Medial

1. Nucleus premammillarius dorsalis
2. Nucleus premammillarius ventralis
3. Nucleus hypothalamicus posterior
4. Nucleus hypothalamicus lateralis

Lateral

5. Nucleus hypothalamicus lateralis

These nuclei correspond relatively closely to those described in the rat by Gurdjian. The lateral nucleus need not concern the authors, as it was not injured in any of their experiments; and in the cat it is apparently not intimately connected with the formation of the periventricular fiber-tracts.

The first of the four nuclei mentioned above, are situated on the lateral wall of the third ventricle and partly on its floor, posterior to the infundibulum. The premammillary nuclei correspond closely to the nucleus tuberis and the nucleus mammillo-infundibularis described by Greving. The anterior part of the nucleus periventricularis posterior also extends into the tuber region. The nucleus hypothalamicus posterior can be traced caudally into the tegmentum of the midbrain and thus corresponds to the nucleus of the same name described by Gurdjian (29), and to the nucleus reticularis of the hypothalamus

mentioned by Greving (28). The nucleus periventricularis posterior corresponds to the nucleus paraventricularis of Greving, and partly to the nucleus medialis hypothalamicus of Winkler and Potter (56).

Each of these nuclear masses sends fibers into the periventricular tracts. Consequently on section of these tracts by a lesion placed in the plane from the posterior edge of the mammillary body to the anterior edge of the superior colliculus, the whole group is severed from the

FIG. 73. A coronal section through the brain at the level of the optic commissure. The degenerated fibers pass laterally, after decussating in the supra-optic commissure. Note the character of the degeneration when the fibers have been cut longitudinally.

lower centres. The five nuclear masses described by Greving, can thus be correlated as follows: nucleus paraventricularis, nucleus mammillo-infundibularis, nucleus tuberis, substantia grisea centralis, substantia reticularis hypothalami, with the nuclear masses of Gurdjian. In the light of recent work along these lines, one of the authors intends to re-investigate the anatomy of this region in the cat.

Pathological Changes at the Site of the Lesion

In all the animals investigated, the lesion was found to be in direct continuity with the third ventricle. The lesion was filled with degenerated tissue in process of being absorbed by phagocytes. These cells were heavily stained by the osmic acid in the slide (Fig. 71). The glial reaction to the lesion was not investigated.

The Degenerated Tracts after Experimental Lesions

In two animals degenerated fibers were traced anterior to the site of the lesion. In Figure 73, appear degenerated fibers which have crossed the median plane in the supra-optic decussation. These fibers, when traced, pass laterally and seem to enter the medial forebrain bundle. It is difficult to say with certainty where they terminate. On examination, it would appear, however, that they make their way to the region of the pyriform lobe.

No degenerated fibers have been traced into the thalamus or laterally into the subthalamic nuclei. Ventral to the lesion (Fig. 71), degenerated fibers can be seen which are crossing the midline in the anterior part of the decussation of Forel. On tracing these fibers, it is seen that they commence on the more ventral aspect of the lesion and, after crossing the midline, pass down the periventricular fibers on the ventral and lateral aspects of the gray matter of the cerebral aqueduct. There is little doubt that the presence of this decussation partly explains the invariable presence of heterolateral fibers in sections caudal to the lesion.

Fibers arising from the caudal part of the lesion pass directly along the outer surface of the central gray matter and continue into the midbrain. These are fine medullated fibers, with a few larger fibers. They do not form large bundles but are spread out in a thin layer. The fibers which have crossed the midline in the decussation of Forel are cut as they arch upwards along the lateral wall of the posterior part of the third ventricle.

When the lesion has been placed in such a manner as to avoid damage to the mammillary body, the mammilothalamic tract remains intact. In one animal, where the lesion passed through the mammillary body on one side, a degeneration of this tract was seen. All the pure hypothalamic degeneration lies medial to the tract and to the anterior pillars of the fornix.

As the fibers pass caudally, they are gathered into a well-defined

but thin bundle on the medial side of the fasciculus retroflexus of Meynert. They enter the midbrain by passing ventral to the fibers of the posterior commissure.

Immediately after entering the midbrain, some of the fibers are seen to pass laterally and to enter the ventral aspect of the superior colliculus, where they apparently end. The remainder commence to arch ventrally, except the more lateral fibers, which enter the dorsolateral part of the midbrain tegmentum in the reticular formation.

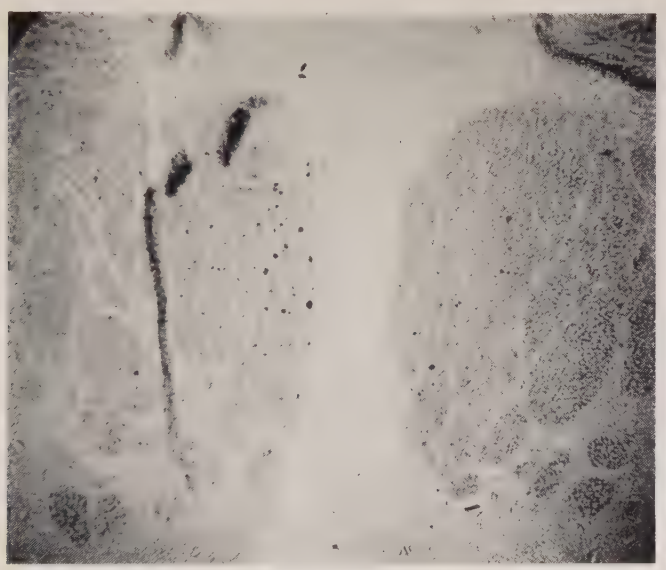


FIG. 74. A section through the posterior longitudinal bundles in the region of the upper medulla, showing some degenerated fibers in the left bundle and a few which are scattered in the substance of the bundle on the opposite side.

In the midbrain, the fibers are in close association with some of those from the mesencephalic root of the fifth nerve, but they are easily distinguished from the latter by their size.

The fibers which pass into the reticular formation seem to end almost at once, for no degeneration can be followed downwards in this region. At the level of the inferior colliculus most of the degenerated fibers are concentrated on the floor of the fourth ventricle, mainly near the middle line where they become confused with the ascending vestibular

fibers (Fig. 74). The more lateral fibers are very much scattered in the dorsal reticular formation (Fig. 75). One gains the impression that in or about this region a further partial decussation takes place, since the number of heterolateral fibers appears to become much greater.

The course of the fibers throughout the pons and medulla remains unchanged from that in the midbrain, with the exception that they

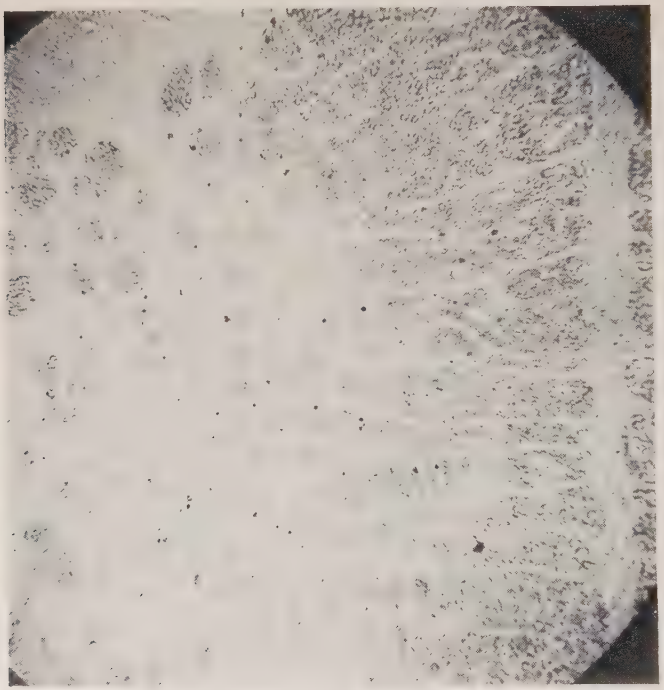


Fig. 75. A section through the posterior longitudinal bundle and the adjacent reticular formation, showing the scattered fibers in the latter region.

become more and more concentrated towards the median plane. In the lower medulla the fibers assume a ventral position, after the decussation of the pyramids. They, therefore, become scattered in the fasciculus proprius anterior and, to a lesser extent, in the more lateral part of the ventral white matter.

In the upper thoracic cord the number of fibers begins to diminish

and many make their way into the gray matter of the lateral horn. In this they apparently descend for a little distance, since fibers cut transversely are frequently seen in this position. The inflow of gray matter into the lateral horn continues throughout the whole thoracic region and caudally into the upper two lumbar segments. In the third lumbar and fourth lumbar segments, the number of fibers is ex-

FIG. 76. A section through the anterior part of the mid-thoracic cord, showing the almost complete equality in the number of degenerated fibers on each side. Note the few fibers which lie in the substance of the gray matter on the right side.

ceedingly small. In one animal at this level (fourth lumbar segment) none were observed (Fig. 76).

The degenerated fibers are small and finely medullated. The Alzheimer-Mann technique demonstrates that the Marchi pictures are not altogether accurate, for many of the periventricular fibers extending as

far as the midbrain have no myelin sheaths. With the former technique the total degeneration appears to be considerably greater than with the Marchi method. The relative position and the termination of the fibers is identical, with both methods of investigation.

Stimulation Experiments

In Part One, the authors have shown that stimulation of a sharply localized area of the hypothalamus will give rise to a cardiac arrhythmia under chloroform. The area stimulated lay in the posterior region of the hypothalamus along a line extending to the opening of the aqueduct from a point about 3 mm. dorsocaudal to the infundibulum. Such an area would correspond closely to the situation of the nucleus periventricularis posterior and the nucleus hypothalamicus posterior. It was noticed that stimulation of the tuber cinereum, produced no pressor effects or extrasystoles, when care was taken to avoid a spread of the current.

Brown and Sherrington (15), working on decerebrate preparations, have shown that pilomotor effects can be obtained by the stimulation of certain regions of the midbrain. When the locus of their stimulation is examined, it is seen that it lies in the fiber-pathway of the hypothalamic nuclei.

COMMENT

The nuclei involved in the lesions which were produced, are confined to the posterior part of the hypothalamus. Bailey and Bremer (6) have shown that the nuclei around the tuber cinereum are concerned with the production of diabetes insipidus. The authors, however, have not been able to produce extrasystoles by stimulation of this region. Posterior to the tuber, and between it and the opening of the aqueduct into the third ventricle, stimulation of the lateral wall of the ventricle gives rise to extrasystoles under chloroform anesthesia and to pressor effects when extrasystoles are not immediately produced. Such a region corresponds to the situation of the nucleus hypothalamicus posterior and the nucleus hypothalamicus periventricularis posterior of Gurdjian (29), and partly to the substantia reticularis hypothalami and the posterior part of the nucleus paraventricularis of Greving (28).

A study of the degeneration shows that a lesion in the posterior part of the hypothalamus, lying medial to the column of the fornix

and to the mammillo-thalamic tract, produces degenerative changes in fibers passing downwards into the thoracic and upper lumbar region. These fibers are partly crossed but mainly uncrossed. They descend beside the lateral and ventral boundaries of the central gray matter of the midbrain, and eventually become concentrated into the more ventral part of the posterior longitudinal bundle and the dorsal part of the reticular formation of the medulla. In the midbrain, pons and medulla, some of the fibers appear to pass out into and end in the dorsomedial part of the formatio reticularis.

The hypothalamic nuclei which have been described above are associated apparently with the medial forebrain bundle and probably with the pyriform lobe; but the latter assumption is as yet uncertain.

The partial decussation of the descending fiber-tracts takes place in many regions; for example, in the supramammillary part of the decussation of Forel and in the upper part of the brain-stem.

The hypothalamus does not send fibers laterally into the thalamus. It has been pointed out above that a section from the anterior edge of the superior colliculus to the optic chiasm, leaves no part of the globus pallidus in the intact part of the brain. Such a section does not abolish extrasystoles nor does it interfere with the reflex production of these abnormal beats, by sciatic stimulation. Consequently it would appear that the hypothalamic nuclei described above are connected directly with the thalamus, and not indirectly through the corpus striatum.

The fibers which pass into the formatio reticularis may assist in the formation of other pathways down into the spinal cord. It was hoped that it might be possible to link these fibers with some of the reticulo-spinal tracts described by Papez (50), but so far the evidence is not conclusive. The existence of such parallel paths would explain the persistence of some sympathetic effects after decerebration. An effect of this nature is illustrated by Cannon and Rapport (22) in their demonstration of the reflex acceleration of the heart after decerebration at the level of the inferior colliculus.

The Marchi method does not offer a conclusive demonstration of the exact termination of the degenerated neurones. These have been traced into the intermedio-lateral column of gray matter and there they apparently end.

It would seem then, that there are some nuclei in the diencephalon which send direct fibers to those columns of gray matter in the spinal

cord known to give rise to preganglionic sympathetic fibers. It is probable that the hypothalamic sympathetic neurones are comparable in some way to the pyramidal nuerones of the cerebrospinal system. There are, no doubt, lower centres which may modify or control the lower neurones in the spinal cord. The results of the above work, however, would seem to show that there is, in the sympathetic system, a cephalization of control analogous to that of the cerebrospinal motor system.

The work cited here, along with that of Houssay and Molinelli (31), and of Karplus and Kreidl (38), would indicate that in the hypothalamus, there are centres for the control of adrenalin secretion. The effect of adrenalin on carbohydrate metabolism is well known and becomes of even greater interest since the publication of the work of Cori and Cori (24). These investigators have shown that under the influence of adrenalin, a shift of glycogen from the muscles to the liver may occur by means of lactic acid.

Furthermore, the experiments of Zunz and La Barre (57) indicate that the blood-sugar level in the cerebral circulation, determines the level of blood-sugar in the body generally. The adrenal glands and the islet-tissue of the pancreas play important rôles in this mechanism. It would be of great interest to determine whether brain-sections, such as those described, would abolish this effect. If this is so, then the paramount importance of the hypothalamic nuclei in the regulation of carbohydrate metabolism, would be established.

As the authors have shown in the present paper, the sympathetic centres of the hypothalamus do influence the heart-rate. It has already been pointed out that these centres can control carbohydrate metabolism. The work of many writers has demonstrated that a disturbance of fat metabolism, water and salt metabolism (diabetes insipidus), also have central representation in this region. Certain emotional states are accompanied by signs of sympathetic activity, cardiac acceleration and pupillary dilatation. There can be no doubt whatever that the sympathetic phenomena of such emotional states must be initiated and controlled by a mechanism at a higher anatomical level than the spinal cord. The work of Bard (12) is particularly interesting in this respect, since he has shown that spontaneous "sham" rage can no longer occur in an animal deprived of its hypothalamus by a brain-section exactly similar to that used by the authors to abolish extrasystoles.

SUMMARY

1. Experimental lesions involving certain nuclei of the posterior part of the hypothalamus are followed by descending degeneration into the spinal cord.

2. The fiber-tracts pass partly into the formatio reticularis of the brain-stem and partly into the intermedio-lateral columns of gray matter in the thoracic and upper lumbar part of the spinal cord.

3. The relation of these fiber-tracts and hypothalamic nuclei to various sympathetic phenomena is discussed.

DISCUSSION

The following questions submitted to Dr. Beattie, Dr. Brow and Dr. Long before the Commission, together with the answers to them, are here reported verbatim.

Dr. Timme: Dr. Jelliffe, may I ask you to open the discussion on this excellent presentation?

Dr. Jelliffe: Apparently, I am the goat of the experimental physiologist.

Dr. Cannon's paper interested me a great deal from a personal point of view. I have had the task of treating cardiac arrhythmic attacks at times (auricular fibrillation). Therefore, I am interested to know what starts them.

In the first place, Dr. Brow said peripheral stimulation will start them. That I can verify because a full stomach will start them. Secondly, he said that emotional stimuli will start them. That I can verify because the efforts of my patients in trying to play a game of chess or a game of bridge, will start them. But the most important thing that starts them, according to my observations, is any hostile activity, not conscious hostility, but unconscious hostility. Perhaps the most striking illustration that comes to my mind at this time is this (and the question will come in later): one patient having been invited to discuss a paper by an acquaintance of his whom he thoroughly disliked because of paranoiac and moronic tendencies, took a long time to make up his mind whether he would or not. He did not. Finally, when the flight reaction took place, he promptly got up a cardiac arrhythmia. Was it possible that the flight as well as the fight started up the adrenal mechanism entirely too much and the patient had a hyperadrenalemia for the time being, and did not need any additional chloroform?

The question interests me greatly and it was partly answered, it seems to me, in the statement that the stimulation may come from different levels, spinal levels, medullary levels, diencephalic levels, and cortical levels; and the proper distribution of the stimuli from the different levels, it strikes me, is a very, very practical question.

The carbohydrate metabolism material is very interesting from the psychiatric point of view. Dr. Singer, I believe, a number of years ago brought to the American

Neurological Association an extremely interesting case of recurrent melancholia, who in the periods when she was well, invariably got up a glycosuria. When she had a melancholia, she had no glycosuria. When she was well, she had a glycosuria. Many times (a dozen times, at least) since that observation was made I have had the opportunity to verify such a type of reaction, especially in these cases of late involution melancholia individuals.

Here again, it seems to me, we have a problem of the aggressive component, namely, the attack upon the adrenal mechanism because, psychoanalytically and psychiatrically, it is known that the depressed patient is one who is filled with unconscious hate, one who would be very, very aggressive if it were not that the aggression was turned upon himself in a suicidal attack. Therefore, it seems to me that the contribution of carbohydrate metabolism is pertinent.

As for the diencephalic centres, I think that Dr. Huber can say much more about them than I can.

Dr. Huber: I am extremely interested, of course, in the work but I must point out again that not only a nucleus or perchance several nuclei are cut in making the puncture in the experiments recorded, but also one or several fiber-paths.

Dr. Cannon: I was especially interested in Dr. Long's work and would like to raise the question whether in Orbeli's experiments (49) and in other experiments in which there is an increase of lactic acid in the muscle on stimulating the sympathetic fibers, the effect might not have been due to a vasoconstriction which would result in a diminished oxygen supply to the muscle.

It has been known for more than fifty years that shutting off the oxygen supply to the liver will cause the breakdown of glycogen into glucose there and it is quite conceivable that the same process would go on in muscle. If that is true, the facts would fit in with the histological testimony which was given this morning.

I was also very much interested in what Dr. Beattie had to say, because he has brought forward quite a new mode of demonstrating reflex secretion of the adrenal medulla. I was in controversy on this question for nearly a decade, and it is very pleasant indeed for me to receive such favorable support for my side.

Dr. Timme: Dr. Beattie, have you anything further to say?

Dr. Beattie: I have nothing to say, sir, except to thank Dr. Cannon for his remarks.

Dr. Timme: Dr. Long?

Dr. Long: If I might comment on the Orbeli work, mentioned by Dr. Cannon, Orbeli has, of course, had that criticism leveled at him before. I think in the muscle that is already contracting, the amount of constriction is more than balanced by the amount of dilatation that you get beyond the arterioles. Whether that is an explanation, I do not know. That is the one fundamental objection to Orbeli's work.

As regards your statement, I was, as a matter of fact, going to call your attention to it, if I had the time. Personally, I think it forms a very good confirmation of your point of view because in our animals in which the heart was completely denervated and which were under chloroform anesthesia, we could only produce extrasystoles by a mechanism which would bring forth a reflex secretion of adrenalin.

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CHAPTER XII

THE PROBLEM OF TONUS IN SKELETAL MUSCLE IN RELATION TO SYMPATHETIC INNERVATION[1]

ALEXANDER FORBES, M.D.

INTRODUCTION

A NUMBER of facts have led physiologists to look on tonus in skeletal muscle as a wholly distinct function from other types of contraction. Many believe that it calls into play a different mechanism from that which produces the simple twitch evoked by artificial stimulation.

Decerebrate rigidity, a state in which the extensor muscles of the limbs remain for a long time in a state of sustained contraction with extraordinary freedom from fatigue, has been taken as the most perfect example of tonus, and has for several reasons been held to exemplify those properties wherein tonus differs from ordinary contraction. In the first place the economy of metabolism and the lack of fatigue and of heat production are so marked, as compared with contraction of the same strength artificially induced, as to suggest the employment of a different mechanism. In the second place, the property of plasticity, as noted by Sherrington (75, 76) whereby a decerebrate limb retains approximately the posture imposed upon it by passive flexion or extension, the extensor muscles maintaining nearly the same tension at various degrees of contraction, suggests a property like that of the so-called "catch muscle" in the adductor mechanism of bivalve molluscs. This "catch muscle," which is distinct from the muscle causing motion, has the power to maintain a given degree of adduction against great tension, for long periods of time without appreciable fatigue. Dynamically it resembles a vise in that it resists great force, but does no work. The superficial resemblance between the plasticity of the decerebrate limb and that of the molluscan adductor has led some physiologists to suppose that the tonus of the decerebrate limb possesses a property of plasticity which is a distinct function from contractility. Furthermore, the

[1] From the Laboratories of Physiology, Harvard Medical School.

failure to detect action-currents in some types of sustained contraction of skeletal muscle, has led many to the view that the tonic type of contraction is one which does not involve the electric response characteristic of artificial tetanus and voluntary contraction.

The work of Boeke (7, 8) and those that have followed him apparently established the innervation of certain skeletal muscle-fibers by sympathetic nerve-fibers. Although the extensive review of Hines (36) brings out the confusing and often contradictory character of the testimony, her summary of the literature, as well as Cobb's (14) and Fulton's ((31), chap. xvi), supports the view that in some skeletal muscles there are striated fibers so innervated. On the other hand, Hinsey (37) was led by a critical survey of previous work and a careful anatomical investigation to doubt the existence of sympathetic innervation in any mammalian skeletal muscle-fibers.

The finding of sympathetic nerve-endings in skeletal muscles naturally led to a search for their function, and in conjunction with the baffling nature of tonus and the apparent need of a special mechanism for its maintenance, predisposed many physiologists to the theory of a tonic function in these nerves. De Boer (9) reported a loss of "tonus" on cutting the sympathetic nerves, and took this observation as a clue to their function. But the observation by both Cobb (13) and Dusser de Barenne (22) that decerebrate rigidity persists after cutting the sympathetic nerves to the limb involved, showed that this type of tonus, at least, does not depend on sympathetic fibers. Indeed the lack of any constant difference between the muscles of the two sides when the sympathetic nerves were cut on one side only, either in the decerebrate or in the intact animal, in Cobb's experiments, and his failure to evoke contraction on stimulation of the sympathetic trunks, rendered it doubtful whether tonic activity of any sort is mediated by these nerves.

THEORIES REGARDING TYPES OF TONUS AND DUAL FUNCTION OF MUSCLE

Langelaan (50) advanced a theory that there are two distinct components of tonus in skeletal muscle, "contractile tonus" and "plastic tonus." Hunter (39, 40) and Royle (73) assumed that Langelaan's theory was well founded and that this distinction was valid. They further assumed that both types of tonus were present in decerebrate rigidity. On this assumption they undertook to determine whether plastic tonus depended on the sympathetic nerve-

fibers. A few of Hunter's experiments on birds and goats appeared to show an impairment of the so-called plastic element in tonus on cutting the sympathetic nerves, without impairment of the so-called contractile element. The experiments on goats were too few to warrant final conclusions on a problem in which so many possible sources of error and confusion are present. The experiments on birds, together with confirmatory experiments by Kuntz and Kerper (47), strongly suggest some such division of function between cerebrospinal and sympathetic nerves as Hunter inferred. Coombs and Tulgan (16) have also reported experiments tending to confirm those of Hunter and of Royle by showing a diminution of tonus in animals, on the interruption of sympathetic innervation. Kuré (48) reports observations on the diaphragm which seem to support this theory; but they do not appear to be very clear cut and should be confirmed before the conclusion is finally accepted. Hines (36) pointed out logical fallacies in Hunter's interpretation of his experiments. Moreover, even if his conclusion were established for birds, it would not be safe to assume that the neuromuscular organization in this respect is the same in birds and in mammals. The attempt to relegate plastic and contractile functions respectively to red and white or fine and coarse muscle-fibers has been shown by Cobb (14), Fulton (31) and Hines (36) to lead only to confusion. Anatomically it is established that red fibers, as well as white, receive somatic innervation. Physiologically it was shown by Hay (35) that red fibers do not act as does the "catch" mechanism, but contract as do the white fibers, only more slowly. This forces the advocates of dual function to place the contractile and plastic functions in the same fiber.

Royle (73), assuming that his own and Hunter's experiments proved the plastic element of tonus to be mediated by the sympathetic nerves, undertook to introduce the operation of ramisection into human surgery, with the idea that, by removing the plastic element in tonus, relief of the condition of spastic paralysis would be effected. He claims to have produced marked and lasting relief by this operation and his claim is reinforced by those of Stewart (77) and Kuntz (45).

Ranson (70), also assuming the validity of Langelaan's theory of separate plastic and contractile functions, experimented with the application of nicotine and chloral hydrate to the spinal ganglia in

decerebrate animals. Finding that both these drugs caused a decrease in decerebrate rigidity before they blocked conduction in the dorsal roots and thereby abolished rigidity altogether, and failing to find any considerable loss of tonus on sympathectomy, he concluded that the plastic element in tonus was mediated by synapses in the spinal ganglia from which the tonic impulses passed antidromically to the muscle, and that only the plastic tonus was abolished by the initial stages of the action of the drugs, while contractile tonus, being mediated by motor nerves, was only abolished when conduction in the dorsal roots ceased altogether. Thus, though he accepts the idea of dual function, he differs from Hunter as to the anatomical structure whereby the plastic function is mediated.

In the foregoing theories it is not made clear whether contractile tonus is supposed to be a wholly distinct function from ordinary contraction. If so, the theories would assign to muscle three distinct functions, phasic contraction, contractile tonus and plastic tonus. The question should be considered as to whether there is after all any sound reason for the assumption of dual or triple function in muscle.

It should be noted that Langelaan's theory of distinct plastic and contractile elements in tonus is a speculation based in part on a misunderstanding of the work of previous observers. His representation of Lucas's observations is misleading in two respects. He cites Lucas as having found three different kinds of *contractile* substance in skeletal muscle, whereas Lucas (55) clearly stated that he found three *excitable* substances, one of which he identified as the nerve-fibers within the body of the muscle—obviously not to be classed as a contractile substance. The contraction of the muscle was the same in Lucas's experiment, no matter what excitable substance was acted upon by the stimulus. Elsewhere the stepwise increase in the muscle-twitch with gradually increasing stimuli, from which Lucas (56) deduced the all-or-none law of muscular contraction, was redrawn by Langelaan as a smooth curve to fit an irrelevant mathematical formula. By such methods he laid the foundation for his theory.

His principal direct evidence for the assumption of dual function in muscle is a record in which a reflex contraction showed a much more gradual onset than did a twitch evoked by a single stimulus applied to the motor-nerve. All the work of Sherrington (frequently misquoted in support of dual function) points to the view that all reflex contractions, whether of abrupt or gradual onset, or sustained as in

tonus, are built up of individual responses of the same fundamental character as that appearing in the twitch. The recent work of Liddell and Sherrington (51) and of Fulton and Liddell (32) furnishes strong evidence that decerebrate rigidity consists essentially of a sustained stretch-reflex, the adequate stimulus to the intramuscular receptors being tension, and involves no other type of muscular response than that which appears in the simple twitch. Fulton ((31), p. 385) contends that "all forms of contractile tension, whether static or phasic, are due to all-or-none contractions of individual muscle units under the integrative control of the somatic nervous system." It should be noted that Sherrington never maintained that plasticity was a separate function from contractility in tonus. He merely called attention to the superficial similarity between the plastic decerebrate limb and the adductor apparatus of the mollusc, in the ability of the muscle in each case to maintain a given degree of shortening, irrespective of the amount of tension. He also furnished evidence tending to show that this behavior was due to proprioceptive reflexes, i.e., reflexes initiated by afferent impulses arising within the muscle involved (cf. also Fulton (31), chap. xvii).

Ranson's experiments (70, 71), taken to support the theory of distinct contractile and plastic elements in tonus, are also capable of at least two other interpretations which involve nothing more than the single and clearly demonstrable function of contraction in skeletal muscle. Fulton ((31), p. 405) suggested that the initial effect of nicotine, when applied to the spinal ganglia, might be the stimulation of afferent fibers which would partially inhibit decerebrate rigidity. Such an effect might be mistaken for the abolition of the alleged plastic element in tonus. Another interpretation of Ranson's observations is based on the probability that afferent impulses follow each other at such high frequency that each occurs in the relative refractory phase following its predecessor and therefore is subnormal (cf. Lucas (57), Forbes and Olmsted (28)). Under these conditions the partial narcotization of that portion of the afferent root comprising the spinal ganglion would suffice to block those afferent impulses arising in intramuscular receptors which reflexly cause decerebrate tonus, before it sufficed to block the full-sized afferent impulses set up by artificial stimulation of the nerve. Thus, while reflexes could still be artificially induced, there would be a partial loss of tonus. At all events, Ranson gives no proof of a qualitative change in tonus; the

observed difference may have been entirely quantitative. It may be concluded that the theory of contractile and plastic tonus as two distinct functions in muscle is absolutely without foundation.

Postural phenomenon. Gessler and Hansen (34) reported that the performance of definite work by human subjects in the long-lasting, so-called psychic, non-fatiguable postures, is accompanied by the same energy expenditure in the state of complete hypnosis as it is in the normal waking state. This postural phenomenon had been taken by some as an example of tonus, distinct from contraction, but the authors conclude that the energy consumption is evidence in favor of the tetanic character of this form of contraction, and does not support the conception of a special tonus function in cross-striped muscle similar to that found in certain postural muscles of invertebrates.

Tonus and contraction. Some physiologists, struck by the apparent contrast between tonus and contractions causing motion, have given great vogue to the theory that tonus is unattended by action-currents, thereby sharply differentiating it from those ordinary contractions evoked by artificial stimuli. Recently the work of a number of investigators, including Dusser de Barenne (21), Buytendyk (11) and others (Forbes and Cattell (26)), has proved that decerebrate rigidity does not depend solely on an action-currentless type of contraction. The clasp reflex of the male frog was at one time taken to be an example of action-currentless contraction, but Wachholder (78) and Lullies (58) have shown that with sufficiently careful experimentation it is possible to detect action-currents in this contraction as well as in other forms of sustained contraction of central origin. The apparent absence of action-currents was largely due to the quiescence of the muscle, an illusion of strong tonus being created by the ready response of the muscle to stretch. When this stretch-reflex was induced, action-currents appeared (cf. Adrian (2)).

Liljestrand and Magnus (52) induced a sustained contraction by the injection of tetanus toxin, and in this condition found an apparently complete absence of action-currents. Ranson (71) made similar observations and emphasizes the absence of action-currents in the contractions so produced. He found that if the motor nerve was cut before the contraction developed, it did not develop at all, but that if severed after the development of the tetanus contraction, the muscle did not relax. This latter stage is a contracture clearly not main-

tained by nerve-impulses. Both Ranson (71) and Fulton ((31), p. 414) infer a direct action of the toxin on the muscle. But Ranson's experiments seem to show that since this contracture does not develop unless it is initiated by nerve-impulses, the local effect of the toxin must be, at most, a minor factor. The most probable inference is that the contraction, induced at first by nerve-impulses, develops through fatigue a state of contracture. It is a familiar classroom experiment to stimulate a muscle to the point of extreme fatigue and observe in this condition the enormous slowing of relaxation. This effect is associated with the acidity caused by activity. It is conceivable that tetanus toxin acts on the neuromuscular junctions in such a way as to abolish their normal propensity for developing fatigue earlier than the muscle and thereby protecting it from overstimulation. The prolonged contraction evoked by the persistent discharge of nerve-impulses from the center would then produce a degree of acidity which would prolong the relaxation time almost indefinitely, and a contracted state without further functional response would be the result.

Action-currents. Pereira (67) attempted to show that the "post-contraction" in man, spontaneously following the cessation of a prolonged, voluntary, isometric contraction (Salmon (74), Kohnstamm, (44)) was a case of action-currentless contraction, but repetition of his experiments with proper controls (Forbes, Baird and Hopkins (30)) resulted in the refutation of nearly every conclusion he drew, and clearly established the fact that postcontraction was exactly like voluntary contraction as regards the action-currents which accompany it.

Thus, with the exception of the pathological contracture induced by toxins, all forms of sustained contraction in skeletal muscle which have yet been carefully scrutinized are characterized by electric responses (see Adrian (2)). These action-currents mark the functional response evoked by artificial stimulation, whether applied directly to muscle or to the motor nerve. They are characteristic of ordinary reflex and voluntary contraction. Insofar as decerebrate rigidity manifests action-currents resembling those of ordinary contraction it appears to involve the same contractile mechanism.

There are certain fundamental theoretical difficulties in the way of accepting either the concept of dual function of plasticity and contractility in skeletal muscle-fibers or the conception of the action-

currentless type of tonic contraction. When a nerve- or muscle-fiber is stimulated a functional response in the form of a propagated disturbance is set up and sweeps over the fiber from the point of stimulation. The exact nature of the disturbance is unknown, but this much is certain, that the energy of propagation comes from the tissue, not from the stimulus, that the available energy is momentarily depleted by the transmission of the disturbance, leaving the tissue refractory to further stimulation until recovery has occurred, and that therefore the response obeys the all-or-none law (Adrian (1), Kato (43), Davis, Forbes, Brunswick and Hopkins (19)). Dynamically the functional response is unlike a sound-wave or other form of vibratory energy in an inert conductor, but resembles rather the burning of a fuse or train of gunpowder. In spite of the many differences between nerve-fibers and muscle-fibers, these fundamental principles apply alike to both. The activity of a tissue which responds in this way cannot be subject to qualitative variation due to any difference in the type of stimulation, any more than the burning of a fuse can be modified by a change in the flame which first ignites it. Any change in the nature of the response must depend on a change in the state of the tissue, such as would be induced by fatigue or an alteration of the physicochemical environment of the fiber. Dual function would demand the presence in the fiber of two distinct excitable structures. Such an arrangement has been suggested in the theory of contractility of sarcoplasm as an independent mechanism distinct from the fibrils. As Cobb has shown ((14), p. 528), there is no physiological evidence of sarcoplasmic contraction; the theory is a purely speculative hypothesis. There is, then, no clear evidence, either anatomical or physiological that there is more than one type of functional response of which muscle is capable. Abundant evidence reveals the essential identity in the nature of responses evoked artificially and by natural means. For instance the action-currents in a motor nerve or muscle appear to have the same character and time relations, whether set up by direct stimulation of the motor nerve or by reflex excitation (Forbes and Gregg (25)); the afferent impulses of muscle-sense are characterized by action-currents indistinquishable from those set up by the direct stimulation of the nerve-trunk (Forbes, Campbell and Williams (27), Adrian (3), Adrian and Zotterman (4)). All these facts point strongly to the view that the functional response of a nerve- or muscle-fiber is always the same in kind, and that the differences between tonic

activity and transient contraction lie in the sequence and distribution of individual responses among the numerous fibers which make up the nerve or muscle in question.

Pollock (68) has recently argued in favor of a plastic mechanism in skeletal muscle, distinct from the contractions and relaxations demonstrably correlated with motor nerve-impulses. Davis and Pollock (20) have reported experiments on decerebrate animals in which, when a muscle was passively stretched and a tonic labyrinthine reflex produced, the muscle shortened with decrement of pull; "but if coincident with production of the tonic labyrinthine reflex at the height of stretch the muscle was further stretched, no shortening occurred and the muscle remained 'pulled out'." (Pollock (68), p. 222.) The opinion is expressed that this was not due to inhibition, and a change in the physical property of muscle is inferred, due to some unknown mechanism quite apart from the presence or absence of motor nerve-impulses. The muscle is said to undergo an alteration which is likened to a change from rubber to gum.

The nature of this observation suggests that it may have been an instance of the "lengthening reaction" previously described by Sherrington (75) and shown by him and by Fulton ((31), p. 431) to be a phenomenon of reflex inhibition, and like all other established phenomena of decerebrate rigidity, dependent on the number and distribution of motor nerve-impulses and the resulting contractile responses. On the other hand, Davis and Pollock (20) state that the tracings from their muscle were similar after the posterior roots had been cut. Whatever lengthening was obtained thereafter was obviously not due to reflex inhibition. The question arises whether their observation could not be interpreted in terms of the viscous-elastic properties of muscle described by Gasser and Hill (33) without the assumption of any new function distinct from its ordinary contractile response.

EVIDENCE SUPPORTING THE THEORY OF ONE TYPE OF CONTRACTION ONLY

Thus far consideration has been given to the experiments supporting the views of Hunter (39, 40) and Royle (73) and the theoretical reasons for doubting them. These theoretical objections are reinforced by the following experimental evidence. Kanavel, Pollock and Davis (42) removed the abdominal sympathetic chain on one side in cats, and at various intervals thereafter decerebrated them by the anemia-

method. No difference, quantitative or qualitative, was found between the limbs on the affected and unaffected sides. They also interrupted the sympathetic innervation of spastic limbs in human subjects without apparent results. Meek and Crawford (62) performed unilateral sympathectomy in a series of dogs and found no demonstrable effects on tonus. Coman (15), experimenting on both dogs and cats, used three methods of attack. His results are summarized as follows:

1. Stimulation of the sympathetic innervation to the foreleg failed to cause any tonic reaction.
2. Complete deprivation of sympathetic innervation to the foreleg failed to influence the normal development of tone either before or after decerebration.
3. Complete deprivation of somatic motor innervation to the foreleg was followed by complete abolition of tone in that leg both before and after decerebration.

RECENT EXPERIMENTAL WORK

A series of experiments was undertaken by Forbes, Cannon, O'Connor, Hopkins and Miller (29), in the hope that by the use of quantitative methods of experimentation small changes in tonus might be detected, if any existed. Hunter (39, 40) and Royle (73) emphasized the need of a lapse of time—several days or even weeks—after interrupting the sympathetic innervation before the full effect of the operation developed. As was pointed out by Cobb (14), Meek and Crawford (62) and Adrian (3) this fact in itself would suffice to rule out the immediate effect of sympathetic nerve-impulses as the direct cause of tonus or of any component of tonus. Any such delayed effect would lead to the view that its cause must be in some secondary effect such as circulatory changes in the muscle. In order to bring out such an effect if it existed, the animals in the series were decerebrated at various intervals after sympathectomy, up to eighty days. In eleven of these the forelimb on one side was deprived of its sympathetic innervation by removal of the stellate ganglion; in the other six, the abdominal sympathetic chain of one side was removed. In three of the animals decerebration was performed first, and then, after observing whether or not decerebrate rigidity was symmetrical on the two sides, the sympathetic operation was performed and the immediate effect of it, if any, was observed. In all the rest of the series the sympathetic operation was performed first aseptically, and after a period of from three to eighty days the animal was decerebrated, and

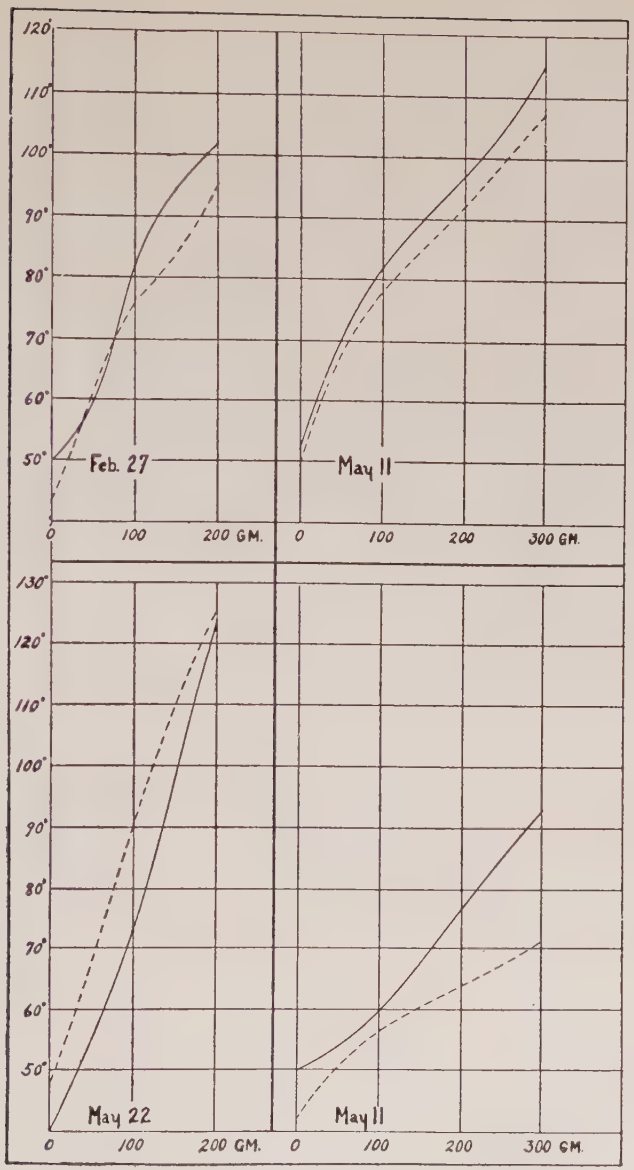

FIG. 77. Chart showing curves correlating elbow-flexion with flexing force applied in stellate experiments: Abscissae, tension applied to wrist perpendicular to ulna; ordinates, degrees of flexion; solid line, limb operated upon; broken line, control. February 27, three days after operation, measurements made one hour after decerebration; May 11, seventy-six days after operation, upper curves twenty minutes, lower curves three hours after decerebration; May 22, seventy-four days after operation, one and one-half hours after decerebration.

the rigidity on both sides was quantitatively studied by means of spring-balances to measure the tension of muscle, and by protractors to measure the angles of the elbow- or ankle-joints.

These experiments showed, in the first place, that if precautions are taken to avoid confusion due to the influence of asymmetrical posture (shown by Magnus and de Kleijn (59) to modify decerebrate

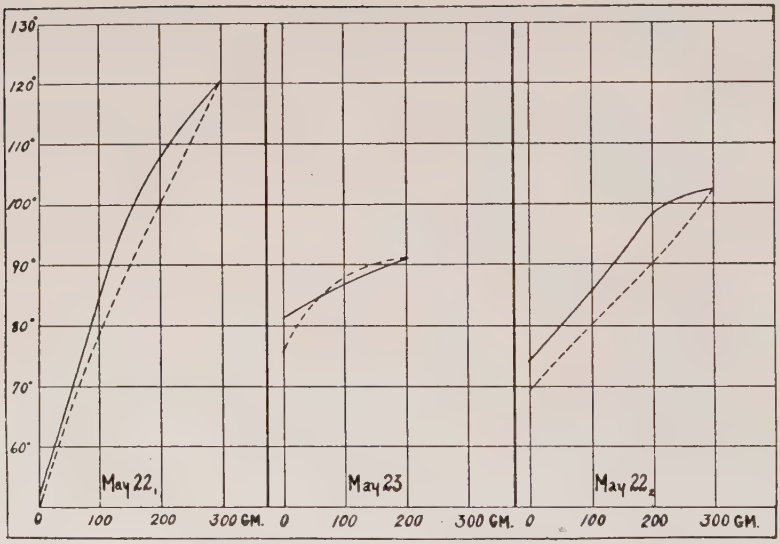

FIG. 78. Chart showing curves correlating ankle-flexion, with flexing force applied in abdominal sympathetic experiments: Abscissae, tension applied to foot perpendicular to metatarsal bones; ordinates, degrees of flexion; solid line, limb operated upon; broken line, control. May 22_1, four days after operation, measurements forty minutes after decerebration; May 22_2, seventy-three days after operation, measurements fifty minutes after decerebration; May 23, sixty-eight days after operation, measurements one hour after decerebration.

rigidity), tonus will usually be approximately symmetrical on the two sides in a decerebrate animal, prior to sympathectomy, and a fairly satisfactory basis can thus be found for testing the effect of operation. But uncontrolled changes in decerebrate rigidity occasionally occur and render the basis of comparison unreliable. A large number of consistent results would be needed to warrant conclusions.

The effects of sympathectomy. As to the effects of sympathectomy,

the results of these experiments were by no means uniform. Comparison of the limb operated upon, with its mate usually showed almost perfect symmetry; that is, no appreciable difference. Sometimes there was a little less rigidity on the affected side, sometimes a little more. The average of the measurements of the entire series showed slightly less rigidity on the side operated upon, but this difference was small compared with the individual fluctuations in both directions making up this average. Typical curves of tonus from these experi-

FIG. 79. Photograph showing appearance of animal two hours after decerebration, six days after left stellate operation. Persistent maintenance of greater rigidity in limb operated upon was noted.

ments are shown in Figures 77 and 78. Figure 79 shows an animal in which the sympathectomized limb, instead of being less rigid, consistently showed more rigidity than its mate. The conclusion from these experiments was that, if there was any loss of tonus in consequence of the operation, it was insignificant. It was found to be extraordinarily easy to produce an illusion of decreased tonus by manipulating the limb upon which attention was concentrated, more than its mate. This effect is presumably due to the operation of the "lengthening reaction" (Sherrington (74)). Certainly, decere-

brate rigidity persisted at least approximately undiminished after sympathectomy, and continued to manifest its plastic features.

Ranson and Hinsey (72) in a series of decerebrate cats, previously sympathectomized, also found no constant difference between normal limbs and those which had been operated upon.

Since these results were published Mortensen, Friedbacher and Quade (63) have reported a careful series of experiments on goats. This is especially interesting, since Hunter's experiments were also performed on goats and the contention was made that these animals are better adapted to bringing out the effects of sympathectomy than the more usual laboratory animals. Mortensen, Friedbacher and Quade found that the changes in limb-tonus due to neck-posture, reported by Magnus and de Kleijn (59), were very marked in the goat and that a very slight asymmetry of position, therefore, confused the result. Making careful allowance for this factor they found in their series no constant or significant difference in tonus between the unaffected and affected sides. Even before the researches of Coman (15), Forbes, Cannon, O'Connor, Hopkins and Miller (29), Ranson and Hinsey (72) and Mortensen, Friedbacher and Quade (63) had been published, Adrian (3), in the course of what is perhaps the clearest and most logical discussion of this subject, said, "On the experimental side then, the balance of published evidence seems overwhelmingly against the view that the sympathetic sends out impulses which have a direct controlling effect on posture, the length or the plastic tone of the limb muscles, an effect comparable to that of the cerebrospinal impulses." With the addition of these four researches the preponderance of negative evidence has become even greater than it was when Adrian discussed the problem.

Ramisection in spastic paralysis. As to the surgical operation of ramisection, several surgeons have been convinced of its efficacy in properly selected cases of spastic paralysis. On the other hand, Crothers (17, 18), who made a careful study of a number of patients operated upon by Royle, was convinced that the beneficial results were either non-existent or else dependent entirely on extraneous factors, such as re-education, good nursing and after-care. Stewart (77) reported favorable results of the operation in a number of cases. His patients undoubtedly showed improvement, but it is perhaps significant that one unsuccessful case reported in his Table 3 is explained away with the foot-note "has not come for re-education." If successful results depend upon re-education, and in the absence of this

are not secured, one wonders if the operation in itself accomplished anything at all, unless perhaps through the psychological effect of making the patient feel that something important had been done. That such an heroic form of mental suggestion might well be eliminated, especially if sufficient care and skill be devoted to the re-education, is strongly suggested by the conviction expressed by one physician of large experience, on seeing the motion pictures of a patient before and after the operation of ramisection, that he could frequently duplicate the result by medical procedures alone.

The researches of Orbeli (66) and Nakanischi (64) may perhaps open a way to reconcile the apparently conflicting testimony of various observers in this field (cf. Martin (60)). Orbeli reports that stimulation of the sympathetic nerves simultaneous with stimulation of the somatic nerves adds nothing to contraction until fatigue appears. With the onset of fatigue, sympathetic stimulation increases the contraction evoked by somatic stimulation. The sympathetic effect shows a much longer latency than muscular contraction evoked by motor nerve stimulation, a latency which approximates that of the action of the sympathetic nerves on the heart.

Nakanischi (64), working on frogs, found that stimulation of the sympathetic nerves alone caused no contraction of the skeletal muscle, but when stimulation of the sympathetic nerves was added to maximal stimulation of the somatic nerve the resulting contraction was augmented. The effect was the same whether the augmenting stimulus was applied to the sympathetic nerve before it joined the somatic nerve or whether the stimulus was applied to the combined nerve distal to the point of junction. Stimulation of the somatic nerve, alternately proximal and distal to the point where the sympathetic nerve joins it, produced identical contractions until the strength of stimulus was increased to a certain value, taken to be the threshold of the sympathetic fibers. Increasing the strength of the stimulus beyond this value caused augmentation of contraction when the stimulus was distal to the point of junction, whereas no change was found when the stimulus was proximal to this point. The author does not appear to have excluded completely the possibility that the augmentation was due to somatic fibers damaged at a point distal to the distal electrodes, so remote from the proximal electrodes that no strength of stimulus applied there was able to excite them, and stimuli at the distal electrodes could do so only when strong enough to cause a considerable current spread along the nerve. On the other hand, the

close similarity of the responses obtained by stimulation distal to the point of junction and by simultaneous stimulation of the separate somatic and sympathetic nerves, renders this interpretation improbable and strongly supports Nakanischi's contention (64) that the sympathetic fibers exert an augmenting effect upon the contraction already established by somatic fibers.

These observations suggest that the nerve-impulses reaching the muscles by the sympathetic fibers act on them in a different manner from the ordinary somatic motor nerve-impulses. Apparently they do not stimulate the muscle; that is, they do not cause contraction. Yet it is conceivable that at the sympathetic nerve-endings a chemical effect of some sort is produced which alters the state of the muscle and, in some way yet to be explained, counteracts the tendency to fatigue, and possibly under other conditions, may augment the contraction evoked through the somatic nerves. Recent observations by Campos, Cannon, Lundin and Walker (12) have shown that adrenin, whose action in general simulates the effect of sympathetic nerve-impulses, although ineffective when given before exercise, can prolong to a remarkable degree the capacity of exhausted animals to continue at work.

Chemical responses to stimulation. These are well known to occur in many different types of cell, as for example all the gland-cells and many of the less differentiated cells involved in repair processes following injury. The migration of phagocytic cells to the site of an inert foreign body can hardly be explained without the assumption that mechanical contact of the foreign body with the adjacent cells stimulates them to produce some substance which attracts the phagocytes by chemotropism (cf. Forbes (23)). There are also the striking experiments of Loewi (53) on humoral transmission of vagus action. These important results have apparently been confirmed by Brinkman (10), Kahn (41), Lambert (49), and de Oliviera Frias (65). In general they show that fluid, perfused through a heart being subjected to vagus inhibition, acquires the property of conferring an inhibitory effect upon another heart through which it is subsequently perfused. Loewi (54) has gone so far as to draw inferences as to the chemical nature of the vagal substance produced in this way. If these effects are definitely established they serve as another striking instance of the chemical effects resulting from autonomic nerve stimulation. More than this they furnish an instance of a chemical effect occurring in a

muscle-tissue specialized primarily for contractile response. There still remains a doubt, however, as to the interpretation of Loewi's experiments. The observations of Asher and Scheinfinkel (6) suggest that the result may be due not to a direct effect of the vagus nerve-impulses, but to physicochemical changes in the fluid surrounding the muscle-fibers caused by a decrease in their contractile activity.[2]

It should be noted that Wastl (79) was unable to confirm Orbeli's observation. Fulton ((31), p. 411) suggests a possible explanation for Wastl's negative results and inclines to the view that Orbeli's conclusions are valid. On the other hand, Porter (69), finding that adrenin does not augment tonic contraction in the decerebrate cat, and arguing from the fact that the effect of sympathetic excitation is elsewhere simulated by adrenin, concludes that sympathetic nerve-impulses have no effect on tonus. In view of such doubts, it is perhaps premature to accept Orbeli's conclusions as established, without confirmation by further experiments.

If such an effect as Orbeli described is indeed a reality it is conceivable that its loss may explain the observations of Hunter (39, 40), Royle (73), Kuntz and Kerper (46) and others who have found changes in tonus following sympathectomy. Impairment of the ability to resist fatigue would tend to diminish the amount of tonic contraction, especially under conditions in which fatigue is likely to develop. It may be that the positive observations have been made under conditions which caused more fatigue than existed in the negative observations. On the other hand, Campos, Cannon, Lundin and Walker (12) found no increased susceptibility to fatigue in running dogs whose hind-limbs were deprived of their sympathetic innervation. Uncertainty as to the conditions favoring fatigue, complexity of the circulatory changes resulting from sympathectomy, and possibly other obscure phenomena are factors that tend to confuse this problem and render it difficult to determine why some experiments are positive and some negative.

[2] Recent observations by Hinsey and Gasser (38), dealing with a slow contraction, apparently without action-currents, in a degenerated nerve-muscle preparation, evoked either by stimulation of undegenerated afferent fibers in the nerve-trunk or by chemical means, are suggestive in connection with the type of function which Orbeli's and Loewi's results indicate. Their bearing on normal muscle is difficult to interpret.

TONUS AND THE ECONOMY OF ENERGY

One of the most baffling features of tonus has been the great economy of energy. In decerebrate rigidity tension is maintained for a long time without visible fatigue, and with very little metabolism or heat-production, as compared with tetanic contraction induced either by voluntary effort or artificial stimulation. This economy has been a major consideration in predisposing physiologists to consider tonus as something distinct from other types of sustained contraction. In an earlier communication (Forbes (24)) it was suggested that this economy might be effected if different groups of fibers took up the load in rotation, each group of fibers possibly being relieved by synaptic fatigue in the reflex arc before the fibers themselves became fatigued, and the next group in turn being called into activity through the proprioceptive mechanism of the stretch-reflex. Adrian and Bronk (5) have just reported some new observations on tonus which give us fresh insight into the mechanism involved. Their new technique has enabled them to observe directly the rhythm of discharge of impulses in a single motor nerve-fiber. Applying this to the limb-reflexes, they have found that a vigorous contraction, in the case of the crossed-extension reflex, is mediated by a series of about eighty impulses per second. In the tonic reflexes, on the other hand, the individual fiber conducts between five and ten impulses a second. Some recent isometric observations, made by Dr. H. Davis in the Harvard laboratory (unpublished), show that a mammalian skeletal muscle, when fatigued, maintains tension more economically if stimulated at a frequency of twenty-five per second than at fifty per second.

In the muscle taken as a whole it is clear from electromyographic studies (Buytendyk (11), Forbes and Cattell (26)) that the individual fiber groups are responding quite out of phase with each other; that is, there is no visible synchronism of response at any such slow frequency as five or ten a second. It is conceivable that the economy may be aided by this asynchronism of individual responses in adjacent fibers. If five maximal stimuli per second are applied to the motor nerve, the muscle soon fatigues. But in this case it contracts as a whole and has time to relax and lengthen after each response; at the next response it must shorten again and do physical work. If, after the contractile effort of each individual fiber, it is prevented from lengthening by friction with an adjacent fiber already in a contracted state, the

contraction will be practically isometric, and the wasteful lengthening will be eliminated. The slow relaxation of the red fibers, as compared with the white, increasing the overlapping in time of contractile tension of adjacent fibers, would serve the purpose of economy.

It may be concluded from this survey of the evidence that in skeletal muscle, instead of three functions, ordinary contraction, contractile tonus and plastic tonus, there is one function—contraction—built of all-or-none releases of contractile energy, but so arranged in time and space by the various reflex influences which play upon the motor centres, as to appear sometimes phasic, sometimes tonic and sometimes plastic.

SUMMARY

1. The evidence from a great variety of researches leads to the conclusion that in skeletal muscle there is only one type of contraction, and that the apparent difference between tonus and other forms of contraction is superficial and not fundamental; that tonus depends for its sustained character and economy of energy upon the sequence of individual responses and their distribution among the numerous fiber groups which constitute the entire muscle.

2. There is no foundation for the view that the sympathetic nervous system controls a plastic element in tonus functionally distinct from so-called contractile tonus. All contraction, tonic or phasic, disappears when the somatic motor nerves are cut. Sympathetic nerve-fibers, when stimulated, do not cause contraction; their severance does not lead to the disappearance of tonus. A large number of researches have been made to test the alleged tonus-maintaining function of the sympathetic nerves. The great majority of them have apparently shown complete absence of any such effect and some of them have revealed sources of error which may well explain the few positive results that have been reported.

3. It is doubtful whether sympathetic innervation has any appreciable effect upon tonus. If it has, the effect must be due either to circulatory changes or to some obscure physicochemical effect of excitation through this channel, analogous perhaps to secretion. There is some evidence that such an effect exists, not causing contraction, but tending to allay fatigue and to facilitate the continuance of contraction evoked through the somatic motor nerves. Although the evidence in favor of such an effect is strongly suggestive, there are

still doubts as to its interpretation, and it is probably premature to accept the effect as definitely established.

4. The surgical operation of ramisection, for the relief of spastic paralysis, rests on a wholly inadequate physiological basis, a basis built of speculation and misinterpretation of experimental evidence. Re-education has been regarded as an important sequel to this operation. In view of the physiological evidence it is perhaps reasonable to conclude that re-education is the only therapeutic agent which has any real effect in these cases.

DISCUSSION

The following questions submitted to Dr. Forbes before the Commission, together with the answers to them, are here reported verbatim

Dr. Ranson: The question has been raised as to the existence of two types of tonus, contractile and plastic. I certainly hold no brief for the separate existence of plastic tonus but neither do I feel that the work of the English school has adequately accounted for the plastic character of such tonic contractions as those of decerebrate rigidity. That plastic character, as illustrated and emphasized by Sherrington, was of such a nature that when a decerebrate limb was passively extended it remained extended, due to a shortening reaction in the triceps. When it was flexed, it remained flexed, due to a lengthening reaction in the triceps.

Lengthening and shortening reactions, therefore, are the very essence of plasticity and I fail to see how they can be explained on the basis of a proprioceptive reflex mechanism.

As a basis of that proprioceptive reflex mechanism, Sherrington has recently set up what he calls the stretch-reflex. When the muscle is stretched, afferents from that muscle reaching the cord set up a reflex tonic contraction. Therefore, when the triceps is stretched in the lengthening reaction it should contract and there should be a shortening, not a lengthening.

I should like to propound that riddle to Dr. Forbes.

Dr. Forbes: Morphologically there are several kinds of receptors in muscle. Fulton takes the position that one of these is stimulated by a mild stretch of the muscle, and induces the stretch-reflex, that is, a sustained reflex contraction. The stretch-reflex is involved in the maintenance of decerebrate rigidity. The lengthening reaction is one in which the resistance of the extensor to passive flexion is overcome by forcible flexion, and then the muscle relaxes and remains in a lengthening condition. This he attributes to reflex inhibition. The adequate stimulus for this is a more powerful stretch than that which evokes the stretch-reflex, and depends, according to Fulton (31), on excitation of pain-receptors. The reflex inhibition which they cause is the dominant reflex.

Dr. Ranson in a previous conversation called my attention to the fact that the lengthening reaction is very easily obtained in the case of some preparations and

with great difficulty in the case of others. This fact does not appear easy to reconcile with the view that pain-receptors cause the lengthening reaction, because, the pain-receptors should be stimulated with the same tension and should produce the same inhibition in the case of the animal with strong rigidity as in the animal with weak rigidity.

I am not sure of the answer to this, but the observations of McCouch, Forbes and Rice (60) strongly suggested that some proprioceptive impulses are set up by tension and others by a change of shape in the muscle, irrespective of tension. If the receptors involved in reflex inhibition were in the latter class they would be protected from stimulation by the sustained contraction of the muscle with the greater rigidity. There are other possible complicating factors, such as synaptic fatigue in some of the reflex arcs involved. Therefore, the ultimate answer to Dr. Ranson's question remains obscure. The main contention I make is that before we postulate a new type of function beyond what is established, we ought to exclude every possibility of explaining the observed phenomena in terms of the known functions.

Dr. Pollock: In a paper that Dr. Davis and I read before the American Neurological Association, we showed that if a muscle stimulated by a tonic labyrinthine reflex in a decerebrate preparation was gradually stretched and the stretch then gradually removed, the muscle did not assume its original length. This is undoubtedly the lengthening reaction. At the same time, the antagonist did not show a reciprocal shortening, but, on the contrary, a reciprocal lengthening. In other words, the lengthening was not the result of inhibition, because at the same time that the muscle lengthened its opponent contracted. Therefore, can you correlate that with the idea that the lengthening of the muscle is the result of inhibition?

Dr. Forbes: I thought at one point you said that the antagonistic muscle lengthened at the same time.

Dr. Pollock: Right.

Dr. Forbes: According to the theory, when the stretched muscle showed inhibition, the antagonist should have contracted.

I do not know how to answer that. Perhaps the reflex was not strong enough to produce the contralateral contraction. It takes a greater stimulus to evoke a crossed-extension reflex than a flexion reflex. Certain conditions in the spinal cord will abolish the crossed-extension reflex while the flexion reflex is still obtainable, and, after all, inhibition is a feature of the flexion reflex.

Those experiments which you described in that last communication are very puzzling, but I am not sure that they cannot be explained in terms of fatigue and the viscous-elastic properties of the muscle (Gasser and Hill (33)), with whatever aid you can get from reflex inhibition.

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CHAPTER XIII

THE INFLUENCE OF THE SYMPATHETIC NERVOUS SYSTEM ON THE CAPILLARIES DURING PERIPHERAL STASIS[1]

J. HAMILTON CRAWFORD, M.D.

INTRODUCTION

WITH the discovery of vasomotor nerves by Claude Bernard (2) the importance of the autonomic nervous system in circulatory regulation came to be recognized. The action of the sympathetic nerves on the arteries and arterioles was definitely established but it has taken many years for any action by them on the capillaries to become accepted. Indeed the capillaries were considered merely passive endothelial tubes whose variation depended upon changes which took place in the other parts of the vascular system. In 1860 Beale (1) described nerves accompanying the capillaries, and Glaser (7) considered these to be sympathetic nerves. The connection of these nerves to the vessel-wall, however, still remains uncertain. Among the early papers Steinach and Kahn (18) presented the most positive evidence that nerve-stimulation could influence the capillaries independent of its action on other vessels. They showed that stimulation of the third, fourth and fifth thoracic nerve-roots at their exit from the cord, produced the emptying of the capillaries in the nictitating membrane of the frog when the circulation was at a standstill. Krogh, Harrop and Rehberg (13) confirmed this by stimulating the lower ganglia (Nos. 8–10) of the sympathetic nerves in the frog and studying the vessels in the web under the microscope. They found that the arteries contracted first, and a few seconds later the capillaries contracted independently. The first evidence of capillary contraction following nerve-stimulation in mammals was presented by Hooker (9) who stimulated the cervical sympathetic nerves in the cat while he watched the capillaries in the

[1] From the Departments of Physiology and Medicine, Long Island College Hospital, Brooklyn.

depilated ear under the microscope. He observed a contraction of the capillaries independent of that of the arterioles. The most conclusive evidence of the independent contractility of the capillaries following nerve-stimulation is that brought forward recently by Harris and Marvin (8). They studied the effect of stimulation of the cervical sympathetic nerves on the vessels in the ear of the albino rabbit. They were able to confirm Hooker's observations but they also showed that stimulation of the sympathetic nerves caused the emptying of the capillaries when the circulation was brought to a standstill by obstructing the arterial supply. Under the conditions of their experiment the effect of contraction of the arterioles or venules on the size of the capillaries would obviously have been to distend them, and not to cause them to disappear. As the result of the investigations described there can be little doubt that the sympathetic nerves can cause contraction of the capillaries independent of their action on the other parts of the vascular system.

The evidence for a supply of vasodilator nerves to the capillaries is much less certain. Doi (6), Krogh, Harrop and Rehberg (13) and Langley (14, 15) have studied this and believe that such a supply exists. They all used frogs, except Langley who used the cat's paw, and found that peripheral stimulation of posterior root ganglia or sensory nerves produced vasodilatation. They endeavored to rule out the action on the arterioles by various means, Doi by dilating the arterioles with acetylcholine and Langley by occluding the circulation before applying the stimulus. Lewis and Marvin (17) repeated Langley's experiment in cats in which the sympathetic nerves had degenerated and they still obtained dilatation.

Knowing the importance of vasomotor reactions to the efficient working of the normal body and having established the powerful influence of the autonomic nervous system on these reactions in all parts of the vascular system, it is important to find out whether variations in these occur in certain pathological conditions in which the flow in the vessels is abnormal. A fruitful field for investigation seemed to be the study of the vascular reactions of the capillaries in peripheral stasis. The abnormality of the blood-flow in the capillaries in cases of advanced heart disease with cyanosis and peripheral stasis has been described frequently. It has seemed to the author that these patients as compared with normal individuals, showed a delayed and even diminished response to various stimuli such as the

sudden change from a hot to a cold temperature or vice versa, or to fright. If this is so, its importance to the organism must be very great. In order to prove this point, the effect of stimulation of the cervical sympathetic nerves on the capillaries of the ear during stasis has been compared with the normal reaction.

EXPERIMENTAL WORK

Albino rabbits of 1.5 to 2 kilos were used for the experiments. Ether was used as the anesthetic. At first considerable difficulty was experienced in obtaining a satisfactory production of stasis. Compression of the veins in the neck proved unsatisfactory, as the collateral circulation was too free. Compression of the base of the ear would have sufficed but by this means a reduction of the arterial supply would have been obtained also. Finally the problem was solved by dissecting out the main ear-veins and producing the requisite amount of traction on them by means of loops of thread passed under the veins. The sympathetic nerve was exposed on the side corresponding to the ear used and was stimulated by faradic current. The ear was fixed flat on the stage of a Leitz microscope and mineral oil was applied to its surface. The magnification used to study the capillaries was 40 times. Light was provided by a 5-ampere direct-current arc-lamp. It passed through a condenser and then a filter which contained a solution composed of a mixture of copper sulphate and potassium dichromate. This solution was green in color so that besides removing the heat rays it provided a better contrast between the capillaries and the tissues than was given when ordinary light was used. The light was reflected from the mirror of the microscope through the rabbit's ear. By means of this method a very satisfactory view of the small vessels in the ear was obtained.

When the preparation had been set up the capillaries were watched under the microscope while an assistant stimulated the sympathetic nerves. The efficacy of the latter was controlled by observation of the pupil. The time during which stimulation was applied, was measured by a stop-watch. At first the changes were studied under normal conditions, then stasis was produced for a period varying from fifteen to twenty minutes and the sympathetic nerves, again stimulated. Finally observations were repeated from time to time after the venous obstruction had been removed. As far as possible the same capillaries were observed during each period.

The following is the protocol of a typical experiment:

Albino rabbit. Weight 1.5 kilos. Ether anesthesia. Main ear-veins in right ear dissected out and loose threads passed around them. Right cervical sympathetic nerve exposed in the neck for stimulation. Right ear placed on the stage of the microscope and examined.

TIME	DURATION OF STIMULATION IN SECONDS	RATE OF BLOOD-FLOW	RESULT
10:31	7	Normal	Contraction
10:33	8	Normal	Contraction
10:35	7	Normal	Contraction
Venous obstruction produced, 10:37			
10:40	13	Capillary observed showed only slight slowing	Contraction
10:42	24	Marked slowing	No contraction
10:46	32	Marked slowing	No contraction
10:51	28	Marked slowing	No contraction
10:57	15	One vessel with slight slowing	Contraction
		Those with marked slowing	No contraction
Venous obstruction removed, 10:58			
11:01	15	Slight slowing	Contraction
11:06	10	Almost normal	Contraction
11:12	6	Normal	Contraction
11:33	8	Normal	Contraction
11:36	7	Normal	Contraction

Four experiments of this nature were performed and all gave the same result. In the normal state that effect was to produce after a short latent period a marked pallor due to contraction of the arterioles. When this occurred the corpuscles in the capillaries became clumped together and the flow stopped. After a short but definite interval the corpuscles again began to move toward the vein and were finally expelled so that the capillary disappeared from view. During this latter period no fresh corpuscles were seen to enter the capillary from the arteriole. There was no doubt that the two changes described were separate processes. The latent period after which these changes took place was practically constant in repeated observations. When

venous congestion was produced the ear became definitely cyanotic. The capillaries were dilated and their flow markedly altered. All gradations were seen between complete stasis and those in which there was little change from normal. The rate of flow was much reduced in the majority of instances and was comparable to the condition which had been observed in advanced cases of heart disease (3, 4).

The flow in the different capillaries varied from time to time as had been seen also in heart cases. The capillaries particularly studied were those in which the rate of flow was considerably reduced. In these no contraction was obtained after stimulation even when it was continued for five or six times as long as had been necessary to cause the disappearance of the capillaries under normal conditions. Some capillaries were observed in which the flow was only moderately reduced and in these, contraction took place after a prolonged latent period. In those in which the flow was almost normal the latent period was only slightly increased. On removing the venous obstruction it was found that gradual recovery took place. Capillaries which had failed to contract during the period of obstruction began to contract after a long latent period. This period became less and less until finally it reached the normal level. (See p. 346.)

There was little doubt that the changes which took place in the capillaries were independent of those occurring in the arterioles. However, it was felt that if a substance could be used which dilated the arterioles but left the capillaries unaffected this possibility could be definitely ruled out. For this purpose acetylcholine was used. Hunt and Taveau (11) first showed the powerful vasodilator action of this substance in extremely dilute solution and Hunt (10) later proved that the action was independent of the vasomotor nerves. Dale and Richards (5) in their classical paper in which they analyzed the action of various vasodilator substances found that this drug acted powerfully on the arterioles but they were unable to find any evidence of an action on the capillaries. They also showed that the changes produced were not dependent on the vasomotor nerves. Acetylcholine has the further advantage that it produces a very marked vasodilatation of the cutaneous vessels. The effect of a single injection passes off very rapidly so that it was necessary to give a continuous injection in order to maintain the blood-pressure low during the entire period of stimulation. A solution of acetylcholine

(1 cc. = 0.002 mg.) was allowed to flow from a burette into the jugular vein at a rate which it had been found in experiments on other rabbits of similar weight would maintain the blood-pressure at 20 to 30 mm. Hg. below normal. It would have been preferable to have had the blood-pressure reading on the animal used for the experiment but the many other details which required attention and the fact that the head was used for observation rendered it advisable to eliminate this detail.

Two experiments were performed in which the procedure was the same as in the previous experiments, with the addition of the injection of acetylcholine during the period of stimulation. As a preliminary acetylcholine was injected in each instance without sympathetic stimulation in order to see whether it produced any action on the capillaries. The only effect observed was a slight slowing of the stream. In some instances it was thought that a slight dilatation took place but this was not constant and, when seen, was so slight that it was uncertain. The differences observed in these experiments from those described above, were that during the normal period the marked pallor due to arteriolar constriction was absent or markedly reduced, while the latent period before contraction of the capillaries took place was about doubled. Stimulation during the period of congestion was without effect on the capillaries in which the rate of flow was greatly reduced, as was found in the other experiments.

COMMENT

The results of the present series of experiments confirm those obtained by previous authors that sympathetic stimulation causes contraction of the capillaries, independent of its action on the arterioles. Not only was contraction of the capillaries produced in the normal animal but it also took place after the arterioles had been dilated by acetylcholine. They also showed that a profound modification of the action of the sympathetic nervous system on the capillaries takes place during stasis. In marked degrees of stasis the capillaries failed to react to sympathetic stimulation and in the lesser degrees of stasis the effect was considerably modified. A similar change has been observed by Lewis (16) in man. He found when the venous pressure in the arm was raised more than 40 to 60 mm. Hg. by means of a cuff that he failed to obtain blanching on puncturing adrenalin (1 : 1000) into the congested area.

It is of considerable interest to study the cause of the altered response during stasis. One possibility is that it may be due to the accumulation of acid metabolites, particularly CO_2, in the vessels and tissue-spaces. This supposition was mainly suggested by perfusion experiments in which capillary-dilatation was produced by acid solutions of much greater acidity than one would find under living conditions. However Krogh (12) has shown that a considerable increase of CO_2 in the circulation is without effect on the capillaries while it required the application of very acid mixtures to the frog's tongue to produce any dilatation of the capillaries. As Lewis (16) points out, it is improbable that an accumulation in the vessels or tissue-spaces of such volatile and weak acids could induce such prolonged effects, as these substances would be rapidly removed when normal conditions were restored. The second possibility that suggests itself is that the profound changes in the capillaries were due to anoxemia. Krogh (12) showed that the changes, which took place in reactive hyperemia following circulatory arrest with complete stasis, were not prevented either in the frog's tongue when it was kept in an atmosphere of pure oxygen so that no cyanosis took place or in the frog's web which was amply supplied with oxygen from the atmosphere. Lewis (16) has demonstrated that this reaction in man takes place after such a short period of stasis as to make it most improbable that it is due to a metabolic change from anoxemia. The third possibility is that it is due to the accumulation in the tissue spaces during the period of stasis of some substances which acts on the capillaries. Lewis (16) has brought forward strong evidence to show that a non-volatile, slowly diffusible substance is constantly produced by the tissues and that it can cause a profound effect on the capillaries when allowed to accumulate. This he terms "H-substance" but he shows that it is probably histamine, as it resembles the latter so closely in its effects. He has also demonstrated that histamine is capable of preventing or abolishing the response of the vessels to adrenalin. This explanation seems to be the most likely for the changes observed in the present experiments. Obstruction of the venous flow would permit an accumulation of the dilator substance, while the gradual recovery observed would be compatible with the removal of a slowly diffusible product, such as the "H-substance."

Although not directly connected with the subject under investigation it was seen that the latent period following sympathetic stimula-

tion before the capillaries contracted was increased when acetylcholine was injected. The changes observed in the capillaries following the injection of acetylcholine, when no stimulation of the sympathetic nerves was used, were very slight and confirmed the view that the arterioles were mainly responsible for the fall in blood-pressure. They did not suggest that the prolonged latent period was directly due to a change in the capillaries. Under normal conditions the arterioles contract after stimulation of the sympathetic nerves and thus prevent fresh blood from entering the capillaries, while after acetylcholine the arterioles remain dilated and allow blood to flow freely into the capillaries. Under these circumstances the capillaries would have a greater force to contract against than when a few motionless corpuscles lie in their lumen. Thus the time required for their complete disappearance would become lengthened.

CONCLUSIONS

1. Peripheral stimulation of the cervical sympathetic nerve, caused the capillaries in the rabbit's ear to contract. This effect took place at a definite interval after arteriolar contraction. It was also present after the arterioles were dilated by acetylcholine.

2. The latent period between the commencement of stimulation and contraction of the capillaries was prolonged when acetylcholine was injected throughout the time of stimulation.

3. Stasis produced by venous obstruction caused either failure of the capillaries to contract after stimulation of the sympathetic nerves or a considerable prolongation of the latent period, depending upon the degree of stasis in the individual capillaries.

4. It is suggested that individuals with peripheral stasis show a variation from normal in their vasomotor reactions, dependent on the degree of stasis.

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CHAPTER XIV

THE INTERNAL SECRETIONS AND THE AUTONOMIC NERVOUS SYSTEM[1]

R. G. HOSKINS, M.D., AND M. O. LEE, PH.D.

THE literature pertaining to the subject of this paper is far too voluminous to be treated *in extenso* at this juncture. The purpose of the authors is to discuss only certain phases of the topic in which they have been personally concerned or which they have at present under investigation. There is a large body of literature that has inferential bearing on this work but only such will be cited as is directly pertinent. The relation of hormones to sympathetic activity will first be discussed after which the parasympathetic system will be given similar consideration.

THE INTERNAL SECRETIONS AND THE SYMPATHETIC SYSTEM

The Adrenal Glands

That epinephrin has a selective, stimulating effect on the terminal sympathetic structures is too well known to require comment. Merely passing mention will be made of the evidence that to a lesser extent the central and ganglionic sympathetic cells are also stimulated. In cases of larger quantities, the vagus seems likewise to be somewhat involved, either primarily or secondarily. The evidence, therefore, is often ambiguous as to whether any given pharmacodynamic effect is to be ascribed to one influence on the sympathetic or a contrary one on the parasympathetic nervous system. A confusing feature of the situation is the fact that epinephrin, like many drugs and possibly all hormones, is biphasic in its activity: it either stimulates or inhibits various structures in accordance with the dosage, hydrogen ion concentration, temperature, initial tonus and other conditioning factors.

Any discussion of adrenal physiology must start from the observations of Addison (1) and of Brown-Séquard (3–5) that adrenal deficiency results in muscular and cardiovascular weakness terminating in acute

[1] From the Memorial Foundation for Neuro-Endocrine Research, Boston.

cases in circulatory collapse. Complementary to this is the well-known fact that epinephrin is a remarkably potent cardiovascular stimulant. When this fact had been demonstrated by Oliver and Schafer (43) the deduction was drawn that the function of the adrenal glands is to furnish a constantly secreted "tonic" whereby the sympathetic system is kept up to an effective standard of activity. The redundancy of such a mechanism from the teleological point of view seems not to have received adequate consideration. It is *a priori* likely that a degree of sympathetic irritability would have been evolved that is adequate to maintain a state of activity consonant with ordinary needs without the necessity of hormone tippling. This consideration points directly towards Cannon's conception (8) of an emergency function of the adrenal medulla and rather throws the burden of proof on his opponents.

Several lines of evidence have led to the conclusion that the so-called tonus theory is untenable. The most convincing is the fact that the destruction of the adrenal glands leads to reduced blood-pressure and other indications of sympathetic failure only after a period of hours or days, whereas circulating adrenalin becomes ineffective almost instantaneously. Hoskins and McClure (27, 28) emphasized the facts that adrenin in minimal (presumably physiologic) doses results, not in a rise but in a fall, of blood-pressure; also, that pressor effects from adrenin can be obtained only at the cost of gastro-intestinal paralysis. Recently Dragstedt (16, 17) and others have published evidence that Hoskins and McClure's observations are valid only in the case of anesthetized animals. They have not, however, controverted the evidence that, clinically, smaller amounts of adrenalin not infrequently lower blood-pressure.

This leads to the hasty consideration of the old-fashioned clinical "hypo-adrenia," a conception that has received much uncritical favor as well as not a little ridicule. The recent observation by Mills (42) of the almost unfailing beneficial effect of small doses of adrenalin by mouth in a sprue-like syndrome encountered in China again raises the issue and serves as a reminder that, whatever may be the findings of pharmacologists in anesthetized and otherwise maltreated experimental animals, "hypo-adrenia" has not yet been convincingly overthrown on its own grounds. Where the burden of proof now lies is beyond the scope of this paper to discuss. That experimental animals can survive and meet the vicissitudes of ordinary laboratory

existence when completely devoid of the adrenal medulla seems to be sufficiently well established. It remains to be determined, however, how well such animals would stand prolonged adverse living conditions such as Mills discusses in his patients.

Granting that the sympathetic system can function satisfactorily without a constant adrenalin "tonic," Elliott (18) made the suggestion that epinephrin serves, not to stimulate, but to maintain the irritability of the sympathetic nervous system. This hypothesis was tested in two ways. Hoskins and Wheelon (31) reasoned that if loss of sympathetic irritability is an essential feature of the picture of adrenal deficiency this should be detectable at an earlier stage than that studied by Elliot in a moribund cat. Accordingly, they determined the responses to sympathetic stimulation in dogs that were showing clearly the characteristic muscular and circulatory weakness of acute adrenal deficiency but that still retained considerable vitality. It was found that such animals give even an exaggerated response to injections of adrenalin or nicotine, hence, the sympathetic system is depressed neither centrally nor peripherally.

Hoskins and Rowley (30) studied the effects on sympathetic irritability of infusing adrenalin slowly by vein. The sympathetic mechanism was tested at the periphery by adrenalin, at the centres by nicotine, in the efferent paths by direct faradic stimulation of the splanchnic nerves and in the afferent paths by faradization of the sciatic nerve. Both adrenalectomized and normal dogs were used. Although there was considerable variability in the phenomenon the paradoxical fact was shown that adrenin instead of increasing sympathetic irritability characteristically lowers it. Attempts to fit this unexpected observation into any of the theoretical schemes of adrenal function have been without success. So far as the authors are aware the observations have received neither confirmation nor consideration since their publication some fifteen years ago.

A further paradoxical element in the situation was introduced by Hoskins' (23) observations that in chronic partial adrenal insufficiency the irritability of the cardiovascular response to stimulation is significantly lessened. He was driven to the less uncomfortable horn of the dilemma, namely, to the assumption that the decreased response under these conditions was a special phase of the general asthenia characteristic of adrenal deficiency and probably to be ascribed to the loss of adrenal cortex rather than to epinephrin deficiency.

The Thyroid Gland

Numerous observers have published evidence that the administration of thyroid substance or clinical overactivity of the thyroid gland leads to augmented sympathetic irritability. So far as acute experiments are concerned Lieb and Hyman (41) have shown that repeated injections of adrenalin, such as have been used ordinarily in investigation of the point, give, as a matter of fact, increasingly larger responses, irrespective of thyroid conditions. This observation casts doubt on a considerable number of the recorded experiments but does not dispose of all of them. Clinical use is made of the assumption of increased sympathetic irritability in hyperthyroidism in the well-known "Goetsch-test." That this test has failed in the hands of many observers to give consistent results may signify merely that both the sympathetic and parasympathetic structures are rendered hyperirritable by an excess of thyroid secretion and hence in element of vagotonia may play a varying part in the composite picture.

Hoskins (24) made a somewhat extensive study of the effect of thyroidectomy on sympathetic irritability, testing the conditions of the vasomotor reflex-arcs in the afferent, central, efferent and peripheral regions, as outlined above. He was unable to obtain any sort of consistent results among the various experimental animals and refrained from publishing the work. His present impression is that the lack of constancy in effects is ascribable to varying degrees of mixed parasympathetic and sympathetic involvement.

The Parathyroid Glands

The fact that parathyroid deficiency results in a condition of generalized neuromuscular irritability is well known. It is *a priori* likely that the sympathetic system would share in this. Direct test at the hands of Hoskins and Wheelon (32) bore out this assumption. The reactions of dogs to adrenin and nicotine were determined by the use of an aseptic technique that permitted the survival of the animals and repetitions of the tests after they had developed typical parathyroid tetany. The evidence was satisfactorily concordant that sympathetic irritability was materially increased.

The Pancreas

The theory that the pancreas and the adrenosympathetic mechanism are functionally antagonistic has had a rather prolonged vogue

and a vicissitudinous evolution. This assumption was a prominent feature in the theories of the Viennese "Wechselwirkung" school of impressionistic endocrinology. The evidence originally cited in support of the theory was tenuous and was subjected to a barrage of contradictory observations and deductions. More recently, however, and especially since the isolation of insulin has afforded a convenient working tool, it has been determined that various results of insulin and adrenalin injections are of opposite trend. Since the evidence now indicates that insulin probably acts predominantly upon the parasympathetic nervous system, discussion will be deferred to a later section of this paper. By direct experimentation, Hoskins and Gunning (26) were unable to detect any significant change in sympathetic irritability in dogs from which the pancreas had been removed.

The Pituitary Gland

In 1912, Kepinow (35) published the conclusion that the injection of small quantities of pituitary extract "sensitizes" the sympathetic system to epinephrin. He observed that there was an augmentation of the mydriatic effect of adrenin in rabbits and cats, a greater vasoconstriction in the Loewi-Trendelenburg frog preparation and an increased rise in blood-pressure, if, immediately preceding the adrenin, a minimal amount of pituitary extract had been administered. Similar observations have been reported by others. Hoskins (22) restudied the problem, using the vasomotor reaction of dogs as a criterion. Standard test quantities of adrenin and nicotine were given intravenously. Then enough pituitrin was injected to give a slight pressor effect. Repetition of the test injections gave precisely the same results as before, hence, at least under the conditions of these experiments, pituitrin has no sensitizing effect on the sympathetic nerves.

That this substance has no direct stimulating effect on the sympathetic nerves, is indicated by the observations of Hoskins and McPeek (29) that the presence or absence of the adrenal glands makes no difference in the vasomotor responses to pituitrin. In a measure this is but inferential evidence, but there is now a large body of data indicating that the adrenal glands share in the response to sympathetic stimulation, hence the absence of any effect on the adrenal glands at least connotes the absence of actual sympathetic stimulation.

The Ovaries

Gynecologists have long been accustomed to assume a special functional connection between the ovaries and the sympathetic nervous system. Perhaps the most convincing evidence of such a relationship is the well-known condition of vasomotor instability that often arises at the climacteric with the presumed ebbing of the ovarian hormones. Hannan (20) has reported that the classic hot flashes can be evoked at will by the injection of adrenin in women at the menopause. That the vasomotor instability can be ameliorated by the administration of ovarian preparations is the only claim regarding the efficacy of such medication that has received any very significant adherence at the hands of competent therapeutists. Even this claim, however, receives far from unanimous acceptance. Unconscious psychotherapy is particularly difficult to exclude here. On the experimental side, Hoskins and Wheelon (33), using the technique previously described, found that the responses to sympathetic stimulation were materially increased in dogs by the removal of the ovaries.

The Testes

Despite age-long observations on the effects of castration and perennial discussion of the topic the actual knowledge of the hormone functions of the testes leaves a great deal to be desired. That castration results in some degree of depression is widely believed. Clear-cut evidence on the point is by no means voluminous. Richter (45) and Hoskins (25) and their co-workers have recently shown by quantitative studies of spontaneous activity that castrated rats, although appearing normally alert and active to superficial observation, actually undergo a three- or fourfold psychomotor retardation. To what extent the sympathetic system shares in this effect could only be determined by direct experimentation. This Wheelon (48, 49), in a continuation of the studies by himself and Hoskins, undertook to do. The reactions of dogs to adrenalin and to nicotine were noted previous to, and subsequent to, castration and after the reception of testicular grafts. The evidence was gratifyingly consistent that the sympathetic system proper, as shown by the reaction to nicotine, became materially less sensitive to stimulation following castration and that the irritability was largely restored in the course of a month or two by testicular grafts.

Other Glands

As far as the authors are aware, the influence of the pineal gland on sympathetic irritability has not been investigated; and the thymus gland has such dubious standing in the endocrine congregation as scarcely to warrant discussion.

THE INTERNAL SECRETIONS AND PARASYMPATHETIC FUNCTIONS

At the present time various problems bearing on this phase of the subject are under investigation in the laboratory. As yet none of the results obtained are ready for final interpretation. Certain data, however, together with results of work by other investigators, indicate that some of the internal secretions have either a pronounced effect upon parasympathetic function, which can be demonstrated experimentally, or else have actions which stand in sharp distinction to effects on the sympathetic system and which are of the sort commonly associated with parasympathetic function. In contrast to the sympathetic, the parasympathetic system stands out as being chiefly concerned with activities tending to the conservation of the animal's energies and the laying up of reserve stores (7, 9). Merely to recapitulate these well-known activities is sufficient evidence for such a statement. The control of the digestive secretions and the movements of the alimentary canal, the control of the oxygen supply to the tissues through the regulation of respiration, the depression of the heart-rate and arterial tension, the probable control of the islands of Langerhans (2, 11, 36, 38), which act to make possible the utilization of ingested carbohydrate,—all are activities which can be somewhat loosely described as *anabolic* in nature. Several of the internal secretions show effects which are likewise essentially anabolic in character, tending towards the conservation and replenishing of the organism. As a matter of fact, only one of the hormones, insulin, has been actually demonstrated to increase vagus irritability.

The Adrenal Glands

That the adrenal glands are closely related to sympathetic function and irritability is well known. There are a few observations to the effect that the parasympathetic nerves are to a less degree stimulated by epinephrin. This statement may serve as a reminder that the much-discussed antagonism between the sympathetic and parasym-

pathetic nerves is only relative and not absolute. Were this not so the final unraveling of the intricate hormone-autonomic relationships would be much more easily accomplished.

The Thyroid and Parathyroid Glands

The trend of direct experimental evidence regarding the thyroid and parathyroid glands, is that they, like the adrenal glands, play a greater rôle in the sympathetic mechanism than in the parasympathetic. It is well known, however, that the thyroid gland has normally an anabolic as well as a catabolic action. Whether this anabolic action is through the agency of the parasympathetic system is very doubtful, although Kalnins (34) has recently found that in small non-toxic doses thyroxin sensitizes the parasympathetic endings in the intestine.

The Pancreas

Much work in the past few years since the isolation of the internal secretion of the pancreas has indicated rather definitely that insulin increases vagus irritability. Santenoise and Tinel (46) and Garrelon and Santenoise (19) reported that the oculocardiac reflex is augmented, the heart- and respiration-rates slowed, arterial pressure decreased and susceptibility to shock increased after the injection of insulin. That the effects were not due to the hypoglycemia was shown by their persistence when glucose was simultaneously administered. Decrease in the heart- and respiration-rates after insulin has also been found by Cunningham and Lee (15). The typical reaction of an animal or person after a large dose of insulin and before the symptoms of hypoglycemic convulsions appear, are indicative of increased parasympathetic action. Some of these are salivation, strong contractions of the stomach and intestines causing hunger pangs, and slowed respiration.

It should be noted that a number of investigators, Collazo and Händel (13), Popper (44), and Labbé (37), have reported negative results in experiments to determine the effect of insulin on vagus irritability. The dosages which all of these workers used, however, were so large that compensatory secondary stimulation of the adrenosympathetic mechanism in all probability was evoked, thus confusing the picture. Cannon (10) has emphasized the significance of this secondary effect.

The Pituitary Gland

As indicated above, most of the work on the pituitary gland has indicated that its effects, so far as they involve the nervous system at all, are chiefly upon the sympathetic; posterior pituitary extract has been shown by a number of workers, Burn (6), Lawrence and Hewlett (39), Heymans and Pupco (21), to be antagonistic in its action to insulin, tending to cause hyperglycemia or a lower degree of hypoglycemia after insulin. Clark (12) on the other hand has reported that these effects do not occur if the liver is not in the circulation, and he believes that there is no reason to suppose an antagonistic action between the pituitary gland and the pancreas. If, as previously stated, insulin is predominantly a parasympathetic stimulant, these facts have some inferential weight as indicating that posterior pituitary extracts primarily stimulate the sympathetic nervous system. The fact that activity of the pituitary gland tends to augment basal metabolism and sugar-mobilization has the same inferential significance.

The Ovaries

From the point of view of the action of the internal secretions on the functioning of the autonomic nervous system, there may be some significance in the fact that there are at least two hormones of the ovary with quite different and in some respects antagonistic action, the corpus luteum hormone and estrus-producing hormone. Furthermore, during each cycle of the activity of the ovary and the reproductive system there are two phases which for want of better terms may be called anabolic and catabolic. During the anabolic phase, there is a slow growth of the system if a corpus luteum is present. This growth consists of a deepening and elaboration of the elements of the uterine mucosa. The same sort of growth takes place under the influence of the corpus luteum of pregnancy. Such a process does not occur if the corpus luteum is absent or degenerates (14). Lee (40) has shown that in the rat during this phase of the cycle, the basal metabolism remains at a rather constant low level. During the catabolic phase of the cycle which is initiated after the sudden degeneration of the corpus luteum there is a correspondingly sudden increase in basal metabolic rate, amounting to a maximum of 12 to 15 per cent.

If the generalization is sound that the parasympathetic system performs conservative functions, while sympathetic activity leads to

expenditure, these facts suggest that the corpus luteum acts synergistically with the parasympathetic nerves.

CONCLUSIONS

The outstanding impression obtained from a survey of the literature is that the relation of the various hormones to parasympathetic activity remains yet largely to be determined. It is remarkable that so few clear-cut studies of the functional condition of the parasympathetic system following the definite increase or decrease of individual hormones have been made. Until such studies have been convincingly carried out there can be little hope of progressing beyond the stage of more or less convincing theorizing.

From the evidence now available one can scarcely escape the conviction that the endocrine glands do play an important rôle in determining the functional condition and the responsiveness of the autonomic system to stimulation. In a broadly general way certain features of synergism or antagonism among the glands can be recognized. There are many important details, however, yet to be determined. In the meantime, it is not wise to be misled into a feeling of false security by premature schemata purporting to set forth these relationships that he who runs may read.

DISCUSSION

The following questions submitted to Dr. Hoskins before the Commission, together with the answers to them, are here reported verbatim.

Dr. Timme: Dr. Hoskins, in the experiments on adrenalectomized animals, can one neglect entirely the minute sources of adrenalin in the body that have not their source in the adrenal bodies and consider such adrenalectomized animals as devoid of adrenalin?

Dr. Hoskins: Obviously, on theoretical grounds one cannot do so. In a good many aspects of research they are negligible. For example, there is not enough of this accessory chromaffin tissue to keep the animal alive after complete adrenal extirpation. However, I think the implication of your question is sound. We do not ordinarily deal with animals completely lacking in epinephrin after these extirpations; and if it be true that only very minute amounts of epinephrin are necessary to maintain irritability, the experiments are inconclusive.

Swale Vincent (47) investigated the amount of chromophile substance in the accessory tissues and found that it was, as a matter of fact, only a very small fraction of that of the adrenal medulla.

Dr. Timme: Then may I ask, further, whether you still hold to your findings of some years ago that small doses of adrenalin have a depressing effect upon the sympathetic nervous system?

Dr. Hoskins: That point has been worked over by a number of investigators lately. Those who have worked with anesthetized animals have confirmed our results that adrenalin under those circumstances is a depressor. Dragstedt (11, 12) and some others have found, however, that this is true only of anesthetized animals. However, clinically, one not infrequently sees a depressor effect from the smaller quantities.

That comes out, for example, in the adrenalin test in catatonic dementia praecox. Typically, one gets a curve in which the depressor phase is the more prominent of the two. In young children, malnourished children especially, the depressor phase often comes out.

The generalization that adrenalin is primarily a depressor agent is not as well supported now as it seemed to be a few years ago but there are still a good many observations in the literature which show that under some conditions, at any rate, in the unanesthetized subject, and particularly in the human subject, epinephrin in small quantities is a depressor agent.

Dr. Timme: That is interesting to me, personally, because at the time of the war we had occasion to examine some fifteen hundred recruits who had been passed by Army Medical Boards as normal and presumably, therefore, they were normal, and they were not anesthetized. The huge majority responded to small doses of adrenalin injected intramuscularly with a depressor effect, a diminution of blood-pressure particularly. As soon as that dose was increased beyond a certain critical point, the depressor effect was not evident and the pressor effect was.

One further question is this: In the pituitary effects on the sympathetic and parasympathetic systems, is there any evidence, or have you any experience as to whether the anterior lobe of the pituitary gland has any depressor effect as distinguished from the posterior pituitary secretion?

Dr. Hoskins: I do not recall any data on that point. The real clinical work on anterior lobe products, I think, is just beginning. We have not had until recently a dependable product for work. Of course, if anterior lobe extract is given intravenously we get depressor effects as we do from liver, muscle or any other non-specific gland material.

Dr. Timme: Lately, the anterior lobe of the pituitary is said to have increased the basal metabolic rate. How that could consistently be put in juxtaposition with the fact that it has depressor principles, is what I was interested in.

Dr. Hoskins: We have some evidence, as a matter of fact, that it does increase the basal metabolic rate.

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CHAPTER XV

VASCULAR INNERVATION OF THE THYROID GLAND[1]

JOSÉ F. NONIDEZ, Sc.D.

INTRODUCTION

IN THE course of work on the nerve-supply of the thyroid, undertaken in an attempt to settle the much-debated question of the existence of secretory nerves in this gland, certain conditions have been found that seem to place secretory control entirely in the blood-vessels. The thyroid gland of dogs was chiefly used, but some material from guinea-pigs was also prepared. The technique employed was the method of Golgi (double impregnation)[2] and Cajal's reduced silver-nitrate procedure (fixation in alcohol-chloral-hydrate mixture).

As shown by the early researches of Crisafulli (6), Anderson (1), Trautmann (13), Berkeley (2), Briau (3), Rhinehart (12), and the recent work of Popow (11), there are in the gland two distinct plexuses of nerve-fibers, namely, the perivascular plexus, specially rich in the arteries, and the interfollicular plexus, represented by fibers running among the follicles. Both plexuses taken from the dog, are seen in Figure 80. The perivascular plexus around the artery, and its branches, is quite elaborate. Collaterals from its fibers leave the territory of the artery, and are lost among the follicles, but some of the fibers of the interfollicular plexus thus originated, eventually reach branches of the same artery, or of arteries in the vicinity, Figure 80, *a*. As will be noticed the interfollicular plexus is not dense, and there are follicles which do not seem to be in contact with fibers.

[1] From the Department of Anatomy, Cornell University Medical College, aided by the Johnston Livingston Fund for Experimental Biochemistry.

[2] Best results were obtained after preservation in a mixture of formalin and potassium bichromate for twenty-four hours. The blocks were then transferred into a 3.5 per cent potassium bichromate solution (for two or three days), then into the osmic-bichromate mixture, in accordance with the rapid method of Cajal. Direct fixation in the latter caused the formation of a fine precipitate along the fibers. Sections were cut from 75 to 90μ thick.

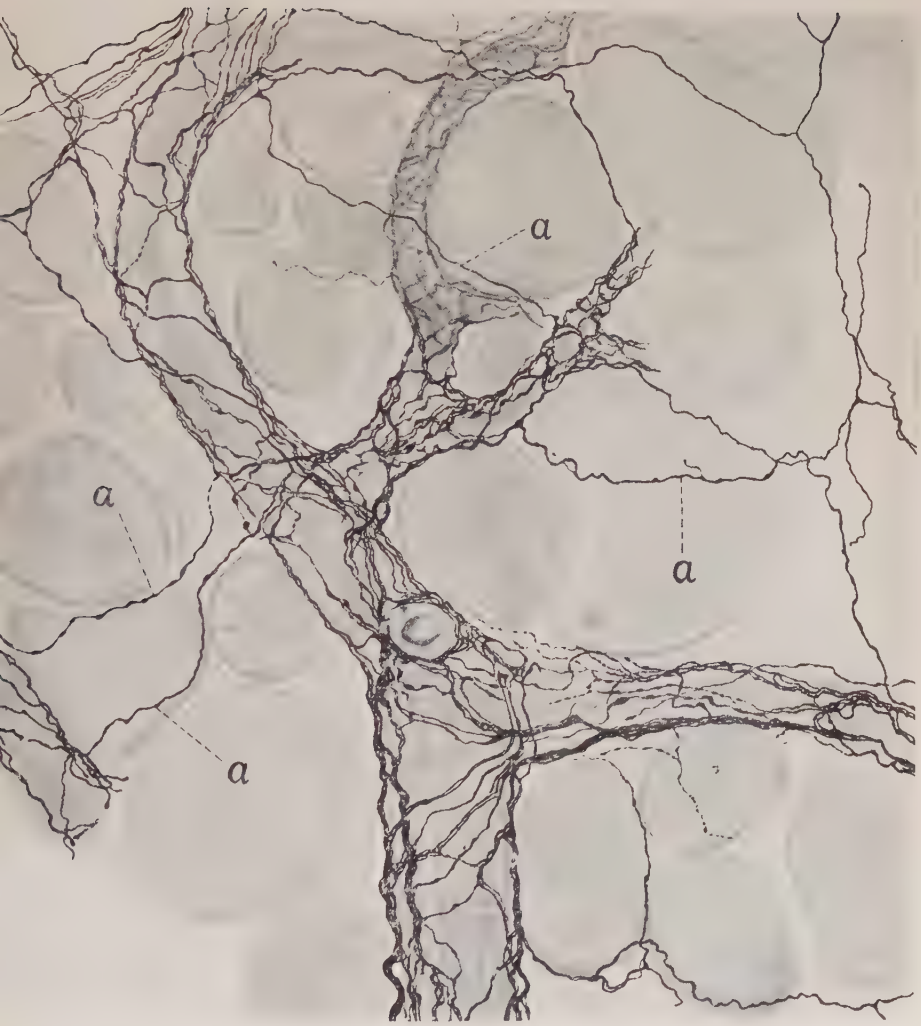


FIG. 80. Perivascular plexus in artery (Dog 1, Golgi). *a*, fibers entering the plexus of branches of the same artery, or of other arteries in the vicinity. (Zeiss obj. 8, ocul. × 5.25)

The prevalent view on the nerve-supply of the thyroid gland, is that the fibers of the interfollicular plexus, or at least some of them, enter into contact with the follicular wall and must be regarded, therefore, as secretory fibers, capable of stimulating the epithelial cells. Thus, Trautmann (13), among the early observers, already distinguished in the thyroid gland two types of fibers, those for the blood-vessels and others that are thinner and longer, and give numerous, strongly varicose branches in the interfollicular connective tissue. These fibers he regarded as specifically glandular. Other investigators, without stressing the morphological differences between the secretory and vasomotor fibers, have also accepted the view that, according to their mode of termination, there are two types of fibers in the gland. The recent work of Popow (11) offers evidence along the same lines, and in most cases, judging from his figures and descriptions, it seems that the fibers regarded by him as secretory belong to the myelinated variety. Without exception, all students of the nerve-supply of the thyroid gland conclude that although there are true secretory fibers in the gland their terminations on the follicles never penetrate between the follicular cells, a fact emphasized by Popow. In this respect the thyroid would differ from other glands (pancreas, salivary, lachrymal and suprarenal glands) in which intra-epithelial terminations have been observed by a number of investigators.

EXPERIMENTAL WORK

Since the existence of true nerve-endings in contact with the follicular epithelium, is of considerable importance from the physiological standpoint, a detailed discussion of the negative evidence furnished by the author's slides seems advisable. Popow found after several trials that the only procedures that gave positive results were the methods of Golgi and Cajal. Without any knowledge of Popow's researches the author has used the same methods himself, as those most likely to yield satisfactory slides. This point is emphasized because it shows that divergences in the interpretation of the facts cannot be due to a different technique.

In common with the older investigators most of the figures offered by Popow as evidence of the existence of secretory nerves in the thyroid, are surface views of the follicles. But Popow, like the earlier observers, seems to have overlooked an important feature. When the surface of a follicle is observed, it is by looking through a network

of capillaries, that usually appear empty or occupied by only a few blood-corpuscles unless there is congestion in the gland. The abundance of capillaries and their arrangement around the follicles is really remarkable. On account of the small amount of interstitial connec-

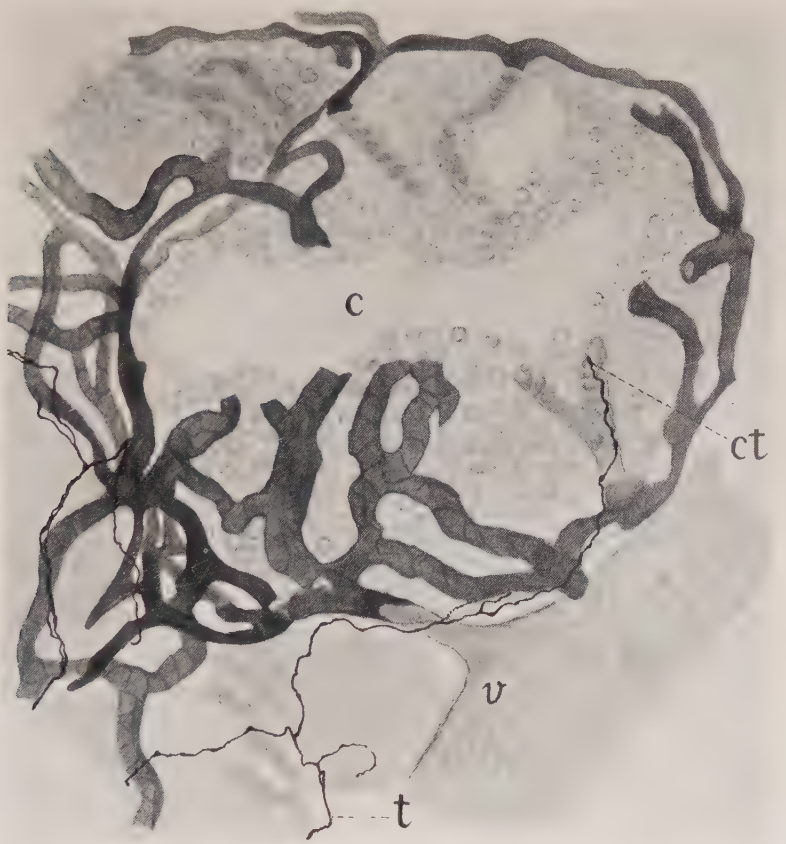


FIG. 81. Capillary network in tangential section of a follicle (Dog 1, Golgi). *c*, colloid within follicle; *ct*, nerve-ending on capillary; *t*, terminal arborization of a nerve-fiber; *v*, vein. (Zeiss obj. 40, ocul. ×4.67)

tive tissue in normal glands, the capillaries are in contact with the basal ends of the follicular cells. The follicles appear as if enclosed in elaborate baskets of capillaries connected with precapillary arterioles and venules, and the capillaries are so close to the follicular

epithelium that in most cases the follicular cells are also seen at the same focus. The capillary network is readily observed in the areas of the sections in which the endothelial lining of the capillaries has attracted the silver, appearing as a coarse network stained from light to dark brown, according to the degree of impregnation.

Figure 81 represents a surface view of a large follicle with a partly impregnated capillary network. Part of the follicular wall was cut off by the knife, disclosing the colloid (*c*) contained within the follicle. On account of this fact the capillary network is also interrupted toward the centre of the follicular surface. As already stated, many of the fibers of the interfollicular plexus represent branches of collaterals or of terminals running among the follicles, to end in other branches of the same artery or in other arterial branches in the vicinity (Fig. 80, *a*). The author is not prepared to state the proportion of fibers ending on blood-vessels, but it is certainly very high. The distances such fibers may cover before reaching their destination is remarkable. In many cases they end on the walls of the veins. The latter have very loose nerve-plexuses; and in the smaller venous branches no plexus really exists, being represented by a few fibers running on the surface of the vessel. The important fact is that while the fibers running among the follicles may touch the basal ends of some of the follicular cells, there are no indications of true innervation. Indeed, no twigs are given off at any point, with a few exceptions of doubtful interpretation, since such twigs may end on empty capillaries. The only signs of innervatory contact are supplied by the varicosities on the fibers, but these swellings, very pronounced in certain slides, less conspicuous in others, are largely artefacts produced by the reagents on fibers that have lost their neurolemma.

Anderson (1) in two of his figures, one from the dog, the other from a human thyroid gland, has represented very elaborate arborizations on the surface of the follicles (perifollicular plexus). Popow clearly states that such a condition must be very exceptional since he has not observed it in his slides. The author, himself, has failed to find similar arborizations, even in the vicinity of the arteries, where the interfollicular plexus is well deveoped. The usual condition shown in the slides is the presence of three to five fibers on the surface of the follicle, that follow a more or less tortuous course. Some of the fibers may divide on the surface of the follicle but the branches are usually so long that their termination is not seen on the same follicle, and in

some cases, it is beyond the microscopic field. Other fibers are, however, shorter and end on the surface of the follicles, but they are far from numerous. One such fiber is seen in Figure 81, *t*. It will be noticed that in this case the longest branch of the arborization sends out two twigs, which end on an impregnated capillary. This branch itself terminates on a capillary filled with blood-corpuscles (*ct*). A second branch to the left of the fiber crosses over a capillary and turns down, ending in another section. Since the publication of Popow's article (9), the author has spent considerable time in a study of the terminations on the surfaces of the follicles, from which he has reached the conclusion that in about 75 per cent of the cases these terminations are in close contact with the capillary wall. But in those cases in which the nerve-ending seems to be applied against the surface of the follicular cells, there is still the possibility that it really lies on the surface of an empty capillary. Furthermore, in sections of follicles there are sometimes nerve-endings placed between capillaries and the basal ends of the follicular cells; under such circumstances, it is obviously impossible to say whether the nerve-ending belongs to the capillary or to the follicular epithelium. However, in favorable cases, it may be seen that there are similar nerve-endings on the surface of the capillary farthest from the follicular wall, while in other instances they occur in capillaries located in thick portions of the stroma, where contact with the follicular cells is impossible. The aspect of the terminal knobs of fibers ending on capillaries can be seen under high power, in Figure 84, *A*. But even where the nerve-endings on capillaries are regarded as secretory nerves, it is plain that if relations of actual contact or of very close proximity are essential for the stimulation of the epithelial cells, then most of the cells in the follicles are not in apposition with the fibers. This behavior is in sharp contrast with conditions as known in other glands in which fibers ending on the secretory wall are very tortuous and send out short twigs that insure contact with practically every secretory cell. De Castro's (5) figures of the nerve-supply of the acini of the pancreas show this point with great clearness. It would appear, however, scarcely safe to regard mere contact, without any indications of repeated and extensive arborizations of the fibers, as evidence of innervation of the follicular cells. The interstices of the thyroid are so narrow that contact of the fibers with the follicles may be only the result of physical limitations. On the other hand the unanimity of opinion of all the students of the

nerve-supply of the thyroid as to the absence of intra-epithelial nerve-endings, further removes the possibility of direct control of the gland by the nerves.

An investigation of the origin of the nerve-fibers ending in the capillaries has shown that they are mostly collaterals and terminals of myelinated fibers. The study of the latter presents difficulties in the case of the thyroid gland.

Very complete impregnations, while disclosing the elaborate vascular plexuses, are really an obstacle in the detailed analysis of the nerve-supply of the gland. But the inconsistencies of the silver-chromate method are of great help, since the impregnation selects certain elements to the exclusion of others in the vicinity, and in such cases the task becomes easier. Thus it was found soon after the work was started that in some areas of the sections only a short number of fibers within a bundle appeared impregnated, and their aspect and mode of distribution led to the suspicion that they belonged to the myelinated variety.

These suspicions were increased after the use of more specific methods, such as Cajal's fixation in alcohol-chloral-hydrate followed by silver impregnation, a procedure that stains myelinated fibers without the impregnation of the plexuses; but final proof was obtained after use of the old, but reliable, method of preservation in osmic acid solution.

In the thyroid gland of the dog and of the guinea-pig there are myelinated fibers ending within the gland. Figure 82 represents these fibers in the dog, in a bundle measuring 26μ in diameter. In the upper part of the figure the bundle appears in cross-section; the lower part is an oblique view of the same bundle in another section of the series. The first fact that attracts attention, is the presence, in this case, of a thick myelinated fiber (measuring 10μ in diameter) that exceeds the size observed in preganglionic fibers (1.8 to 3.6μ, according to Gaskell (8), p. 15). Three other fibers of smaller diameter also appear in the figure.

In slides impregnated by the method of Golgi the myelin sheaths, although not blackened by the osmic acid in the hardening mixture, are fairly well seen under proper conditions of illumination. But aside from the actual observation of the myelin sheath there are other characteristics that permit identification of the fibers under discussion. As shown in Figure 83 *A*, the myelinated fibers (*m*) possess a very

smooth outline and are quite wavy. Non-myelinated fibers (n) are usually more varicose and more tortuous, and in most cases, they are also thinner. While in A the myelinated fibers do not show any collaterals, some of the latter are seen in B. In this figure there is a thick, myelinated fiber, m, and two thinner fibers of the same variety (m', m''). The former divides at the level of bifurcation of the artery;

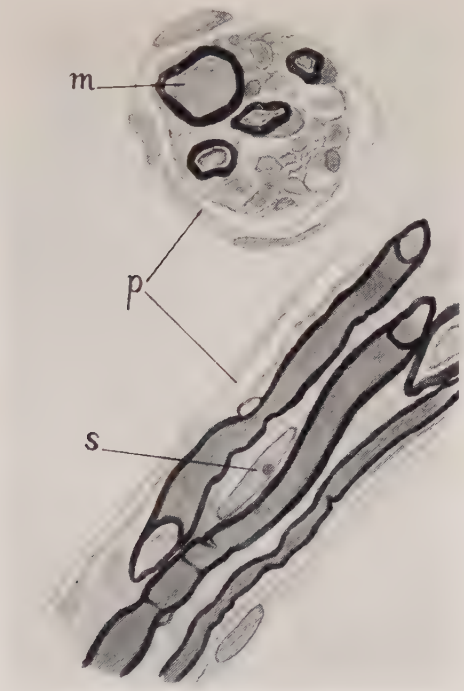


FIG. 82. Myelinated fibers in nerve-bundle of thyroid (Dog 5, osmic acid solution). m, large myelinated fiber; p, perineurium; s, nucleus of cell of Schwann. (Zeiss obj. 1 mm. 2 mm., ocul. ×15.)

one of the branches is interrupted at a short distance from its origin, while the other breaks up into an arborization that is soon lost in the impregnated plexus on the arterial branch (not represented in the figure). The fiber, m', gives off a collateral (c) that runs along the artery and follows one of the branches of bifurcation.

Finally, the fiber, m'' sends out a collateral (c') that follows one

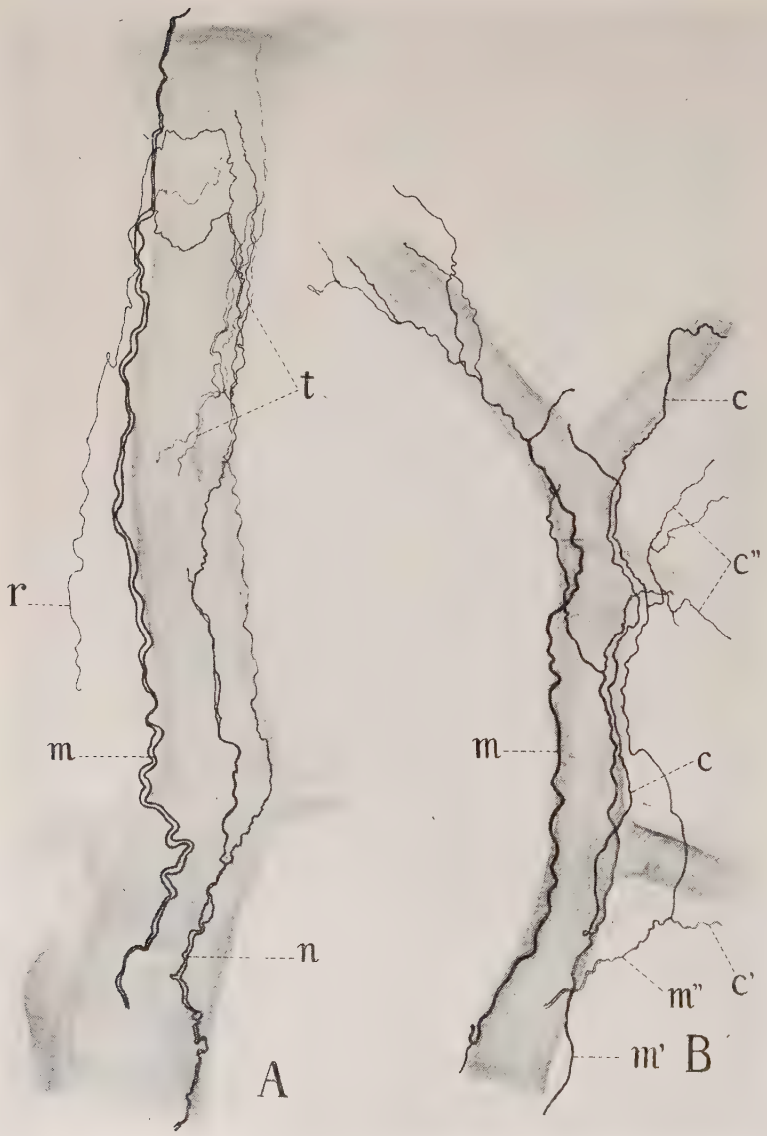


FIG. 83. Myelinated fibers in arteries. (*A*, Dog 1; *B*, Dog 5, Golgi). *m*, *m'*, *m"*, myelinated fibers with *c*, *c'*, *c"*, their collaterals; *n*, non-myelinated fibers with their terminations, *t*, on arterial media; *r*, a recurrent branch of termination, *t*. (Zeiss obj. 8, ocul. ×7.5)

of the arterial branches, and a second one (c'') that soon breaks into a varicose arborization. From this evidence, and other cases that might be cited, one is forced to the conclusion that the myelinated fibers of the thyroid gland closely follow the blood-vessels, and that their collaterals fail to leave the territory of the vessel before final arborization. The smooth outline and the wavy course of the myelinated fibers permit their identification in cases in which the vascular plexuses are not very close; often they are wound around the vessel in a spiral. Yet, although one might at first be tempted to conclude that the myelinated fibers supply the arteries, they do not seem to take part in the formation of the plexuses, with the possible exception of the small arteries and arterioles. Their field of distribution is mainly outside the arteries, in the capillary networks already mentioned. In slides stained by Cajal's method, after preservation in alcohol-chloral-hydrate mixture, the distribution of the myelinated fibers along the arteries is also very conspicuous. In the guinea-pig, for example, in which it is possible to cut sections of the whole gland, the extent of their distribution from the main arterial trunks to the smaller vessels in the periphery of the gland is brought out with utmost clearness.

Figure 84 *B* represents the termination of the vascular plexus in a precapillary arteriole (a). It will be noticed that there is one fiber that runs beyond the point where the vessel loses its muscle-coats (f), and that there are endings in both the arteriole and the point of origin of two capillaries. Figure 84 *C* shows an arteriole (a) breaking into capillaries, clearly seen in this case since they appear impregnated. Termination of a fiber on a capillary is noted at t. Unfortunately, in these, as in many other cases, it is impossible to state whether the fibers represented are terminal branches of unmyelinated fibers or whether they belong to the non-myelinated variety, since the myelin sheath is lost at the terminal arborization.

Ganglion-cells in the thyroid gland were described by some of the early investigators (Peremeschko (9), Poincaré (10), Crisafulli (6)), but their presence was denied by others (Zeiss (14), Anderson (1), Trautmann (13), Berkeley (2), Brian (3), Rhinehart (12)).[3] The

[3] Peremeschko (9), Zeiss (14), and Poincaré (10), used the method of maceration and staining with fuchsin. The other investigators used chiefly the method of Golgi. The well-known tendency of this method to produce precipitates may have led most of those who employed it to the belief that real ganglion-cells are deposits of silver-chromate at the intersection of fibers.

latter view has been shared by Popow (11) in his recent articles. While it is true that the elements regarded as ganglionic by Peremeschko

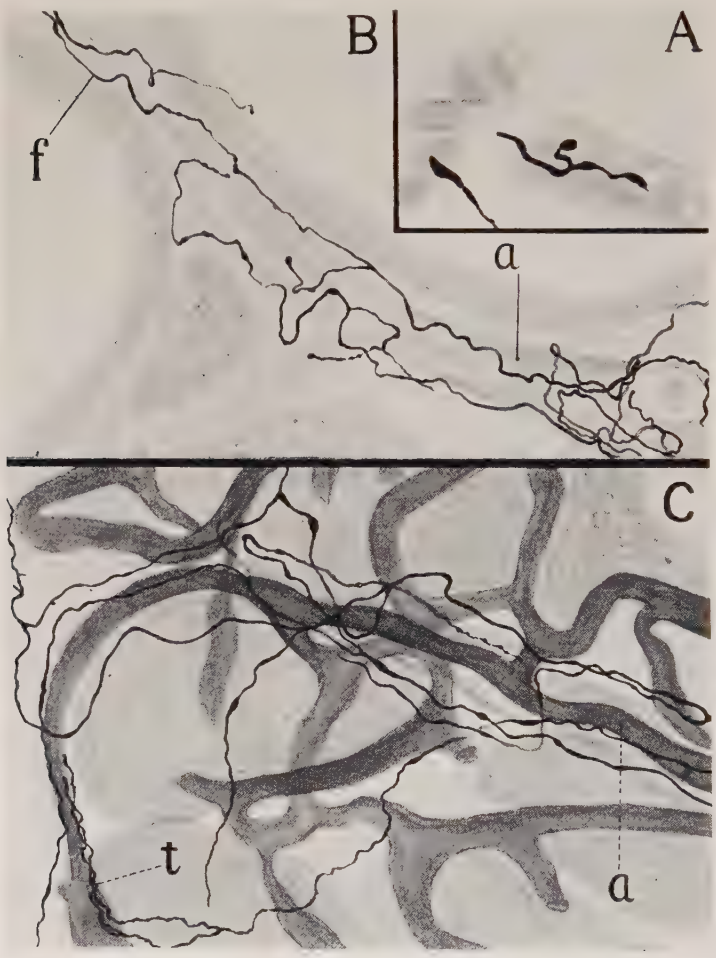
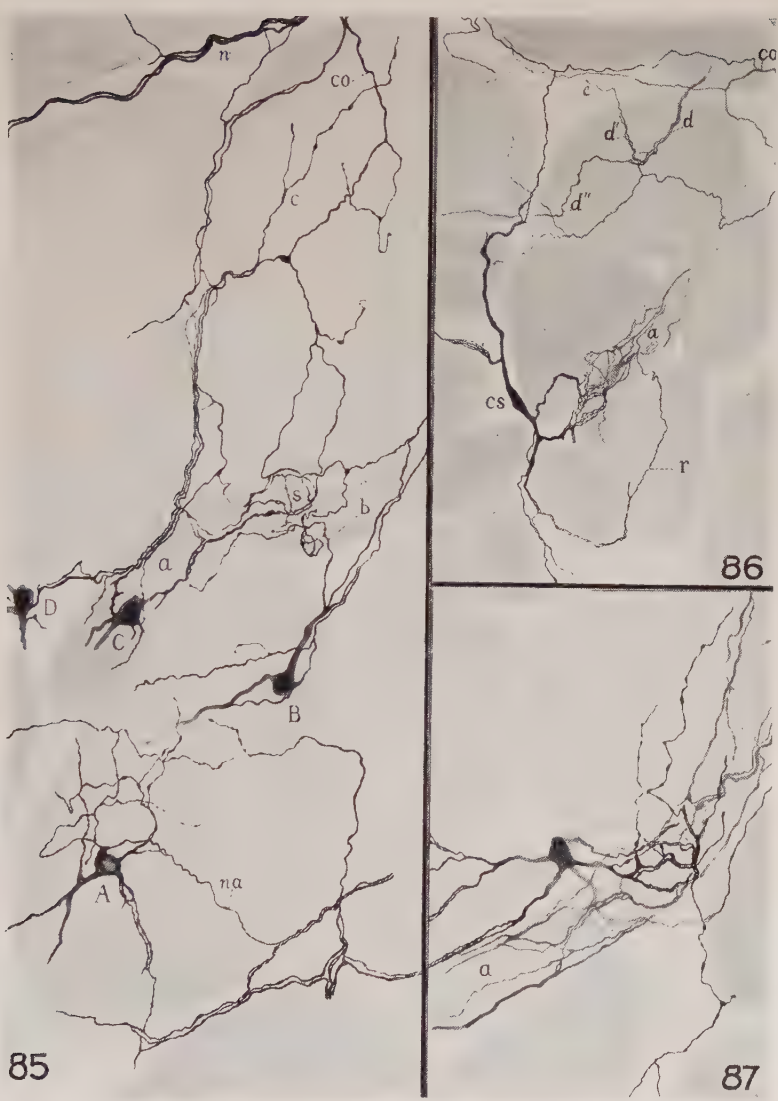


FIG. 84. *A*, nerve-endings on capillaries. *B*, fibers on arteriole, *a*; *f*, fiber following capillary. *C*, impregnated arteriole, *a*, breaking into capillary network; *t*, endings on capillary. (Golgi, *A*, Zeiss obj. 40, ocul. ×11.25; *B* and *C*, obj. 40, ocul. ×5.25.)

(9) are undoubtedly cells of the perineurium, and that precipitates at the point of bifurcation of the fibers, or in the capillaries, may



FIGS. 85, 86 AND 87. Ganglion-cells in thyroid gland, *a*, arteries; *b*, terminals of a dendrite from cell *B*; *c*, terminals of a dendrite from cell *C*; *co*, collaterals from nerve-bundles; *cs*, spindle-shaped cell; *d*, *d'*, *d''*, dendrite and its branches; *n*, nerve-bundle; *na*, dendrite resembling a neuraxone; *s*, area of proximity of dendrites and collaterals on surface of artery. (Fig. 6, Dog 2; Fig. 7, Dog 1; Fig. 8, Dog 2.) (Zeiss obj. 40, ocul. ×15.6.)

closely simulate ganglion-cells, there can be little doubt that the latter exist normally in the thyroid gland. A few of the ganglion-cells found in the course of the author's work have been represented in Figures 85, 86 and 87, drawn from the dog.

Figure 85 represents four ganglion-cells in the same field. Owing to the weak impregnation of the cell-body and the bases of the dendrites the nuclei are visible in the four cells, especially in *A*. The latter sends a long process (*na*) resembling a neuraxone that enters a bundle of fibers crossing in the vicinity. Some of the dendrites of cells *B*, *C* and *D*, reach the wall of an artery, where they meet the aborization of collaterals (*co*) arising from a bundle of fibers (*n*), contact or very close proximity being effected in the areas, *s*, of the artery. Unfortunately, it is impossible to state whether the collaterals arise from a myelinated or a non-myelinated fiber.

Figure 86 represents a spindle-shaped ganglion cell (*cs*) deeply impregnated. It will be noticed that two of the dendrites divide profusely in the wall of a small artery (*a*), while another (*r*), representing a secondary branch, courses around one follicle and finally enters the arterial plexus.

Figure 87 shows a third example of the ganglion-cell. In this case the cell is in close proximity to an artery that receives many of the dendrites, but as will be seen, there are also dendrites that leave the arterial plexus and are lost among the follicles.

Some other convincing examples might be illustrated but the author believes that those shown in the figures furnish sufficient evidence of the presence of ganglion-cells in the thyroid gland. Popow (11) suggests that impregnated cells occurring in Golgi slides are connective-tissue cells. The author has examined some areas in the vicinity of the large arteries where the elastic fibers were faintly stained, without being able to discover a single impregnated connective-tissue cell. Furthermore, connective-tissue cells with branches as long as those in the elements represented in the figures, are unknown; and if it could be proved that the cells represented belong to connective-tissue, their presence in the thyroid gland would be a feature not found elsewhere in the organism.

At present it is impossible to say whether the cells under discussion possess a neuraxone. Their size and aspect, and the absence of a capsule around the cell-body, lead to the belief that they are elements closely allied to, and perhaps identical with, the cells of the plexuses

of Meissner and Auerbach in the intestine, and to the scattered ganglion-cells found in the pancreas by Cajal (4). These cells do

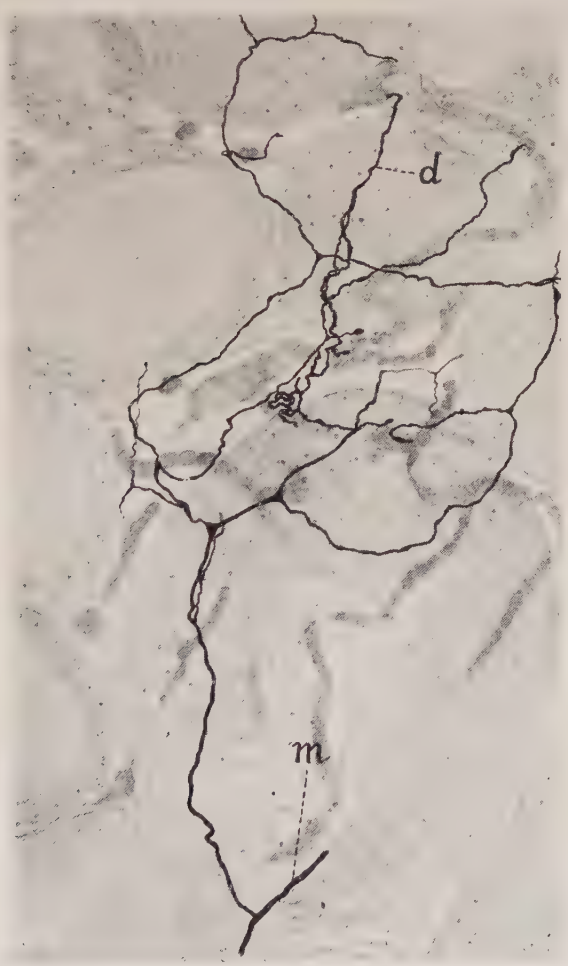


Fig. 88. Collateral from a thick myelinated fiber. *m*, showing relations of contact with a fiber, *d*, presumably a dendrite of a ganglion-cell. (Dog 5, Golgi.) (Zeiss obj. 40. ocul. ×11.25.)

not possess differentiated neuraxones, and they also lack a capsule. They seem to belong to a very primitive type of neurone, and their

presence in such different situations as the thyroid gland, digestive tract, and pancreas, is not surprising when one bears in mind the close ontogenetic relationship of these organs. The dendrites of the cells in the thyroid gland, measure in some instances from 500 to 600 μ, and, in a few cases, they are even longer.

The connections of the ganglion-cells are of great importance. Unfortunately these elements are difficult to impregnate by the method of Golgi, especially the cell-bodies,— a fact which may account for the failure of most of the investigators to recognize their presence. The evidence at hand points conclusively, to the participation of some of the dendrites in the formation of the arterial plexuses, the dendrites running along with, and often twisting around, the finer branches of the non-myelinated fibers. Similar relations of contact are often observed in dendrites coursing along the collaterals that issue from fibers in the bundles. The clearest case of this kind is seen in Figure 86, where a branch (d') of what there is every reason to interpret as a dendrite (d), is twisted around a branch of a collateral (c) which has issued from the plexus of an artery in the vicinity. Similar twistings are abundant in sections with impregnated ganglion-cells, strongly suggesting some sort of synaptic association.

In Figure 88 the author has represented a collateral from a thick myelinated fiber (m). Of special interest is the presence of a fiber (d) which in the territory of the collateral sends out small, robust twigs, seemingly articulated with one of the branches of the collateral. Whether the fiber under discussion is a dendrite of a ganglion-cell or part of the terminal arborization, it is hard to say. Similar conditions have been observed in many other instances.

From what has been said it is clear that the thyroid gland possesses three types of elements, namely: (a) non-myelinated fibers forming the bulk of the nerve-supply of the gland; (b) myelinated fibers of unknown origin; and (c) scattered ganglion-cells of the type found in the enteric plexuses. Although the author is not prepared to draw definite conclusions as to the mode of articulation of the three types of elements, the necessity of formulating a working hypothesis for further work along experimental lines has led him to form provisional conclusions based on the strength of the histological study of the normal gland. These conclusions are, of course, subject to revision.

CONCLUSIONS

Myelinated fibers. The myelinated fibers distributed along the vessels in the thyroid gland suggest that the latter may receive parasympathetic innervation. This view, however, is not entirely satisfactory, inasmuch as the ganglion-cells observed in the gland are not so fully differentiated as are the cells of sympathetic ganglia in other parts of the body. But while the small myelinated fibers may be preganglionic, the larger myelinated fibers measuring about 10 μ in diameter should be interpreted as afferent fibers. Popow (11) has observed peculiar nerve-endings in the stroma and he ventures the view that such structures may be classified as *sensoreceptorische* endings. It is quite possible that the large myelinated fibers end in the stroma and that they belong to the proprioceptive pathway, while the smaller fibers end on the capillaries; but this point has yet to be proven.

Dendrites. The abundant dendritic contribution of the ganglion-cells to the arteries the author is inclined to regard as a very important feature. In the hypothesis under consideration such cells would receive impulses from dendrites twisted around the terminal branches of the afferent fibers, and would transmit them to the walls of the blood-vessels. Such impulses might be of an inhibitory nature, and acting on the smooth muscle-cells in the arterial walls, they would tend to block temporarily any impulses reaching the muscle-fibers from the sympathetic nervous system. An arrangement of this kind, if it exists, would largely eliminate the longer reflex arcs and would provide for an autoregulation of the circulation within the gland. Since the injections of adrenalin cause vasoconstriction in the thyroid gland, it does not seem unlikely that the arrangement suggested would tend to emancipate the gland from the action of adrenalin or of the prolonged excitation of the sympathetic fibers ending on its vessels.[4] The initial stimulus received by the dendrites of the ganglion-cells could be imagined as either of chemical or of mechanical nature, i.e., caused by the dilatation or contraction of the capillaries. Thus the ganglion-cells in the thyroid gland would function not as direct receptors of stimuli, but as connectors, estab-

[4] The finer branches of the perivascular plexus lie on the surface of the muscle-coat of the arteries and their purpose is certainly the innervation of the smooth muscle-fibers, as is the case in other parts of the body.

lishing a link between the specialized nerve-endings of the afferent fibers and the muscle-fibers in the arteries. If the stimuli received are of sufficient intensity, they may reach the central nervous system through the afferent fibers, and be part of a longer reflex arc in which the central nervous system and the sympathetic ganglia would be involved.

The mechanism so briefly sketched would eliminate, at least in the case of the thyroid gland, the obscure axone-reflexes advocated by many authors in order to explain local changes in the capillaries after the afferent part of a reflex arc has been discontinued.

Thyroid secretion. Finally, from the lack of nerve-endings on the surface of the follicles one would infer that thyroid secretion is indirectly regulated by the nervous system through the blood-vessels. Vasoconstriction and vasodilatation would thus be of the utmost importance in the stimulation and depression of the gland. The short reflexes mediated through the ganglion-cells, invoked in the working hypothesis suggested above, would influence secretory activity in localized areas of the gland without interfering with the same activity in other areas. It can be conceived that the suggested arrangement would tend to keep the hormonic output of the gland within a certain level, which is certainly much below that reached when the whole gland is in activity. This would also explain the reason why it is possible to extirpate large portions of the gland without considerably decreasing its function to any great extent. The thyroid gland, like other endocrine glands, is actually producing much less secretion than it is capable of elaborating; because instead of the simultaneous secretion by all of its cells, there are probably waves of stimulation which are inhibited in some areas by the action of the ganglion-cells on the musculature of the arteries.

DISCUSSION

The following questions submitted to Dr. Nonidez before the Commission, together with the answers to them, are here reported verbatim.

Dr. Cannon: I regret very much that I have never had the discipline which would allow me to make a critical comment on these very interesting observations.

There is a question I should like to ask and that is whether there has been any use of the same method, precisely the same method, in studying histologically a secreting system like the adrenal medulla, for instance, which we know has secre-

tory nerve-fibers distributed to its cells. I wonder whether the same method would show similar conditions to those you observed in the thyroid gland?

Dr. Nonidez: The method of Golgi was used by Dogiel (7) in his study of the nerve-supply of the adrenal gland, and more recently by de Castro (5) in his work on the innervation of the islands of Langerhans. In both cases, nerve-endings in contact with the secretory epithelium were found, as well as intra-epithelial (hypolemmal) endings.

I should like to say that histologically the medulla of the suprarenal gland shows evidences of a real secretory innervation by means of the nerve-fibers ending on the epithelium, which are probably independent of the fibers that supply the vessels.

More recently, de Castro has found terminations in the case of the islands of Langerhans, which are independent of the nerves ending on the vessels and of those supplying the pancreatic alveoli. The fibers ending on the cells of the islands, like the fibers ending in the medulla of the suprarenal gland, may convey impulses to the secretory cells and may increase their activity, as Dr. Cannon has pointed out so well this afternoon (pp. 181–198), and these are what we might call emergency fibers.

According to my conception, there are two types of glands: (*a*) those that produce an abundant secretion within a short time and have direct nerve-endings on the cells; while there are other glands (*b*) which secrete slowly and would depend almost entirely on vascular innervation. The thyroid is one of those slowly-secreting glands that has no specific innervation for the epithelial cells.

Dr. Ranson: The only question I would raise is along the same lines as that one asked by Dr. Cannon, and it is with regard to the method. I am not sure that I followed the paper closely enough to hear, but I should like to ask if you used any other method besides that of Golgi, such as the Bielschowsky method, the Cajal method, or the methylene-blue stain? I feel that these other methods are rather more reliable for the purpose than is the Golgi method.

Dr. Nonidez: I used the method of Cajal for the staining of myelinated fibers (fixation in alcohol-chloral-hydrate mixture). Popow (11) in his work on the nerve-supply of the thyroid has used a number of methods, but he found that the only procedures that yield satisfactory results are the methods of Golgi and Cajal. I used these methods from the beginning as those most likely to give results. Nerve-fibers can be traced for some distance on Golgi slides since the sections are cut thick (90 or even 100μ). In methods requiring thinner sections, this is impossible since the fibers are very wavy, and run in different planes.

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Section IV

EXPERIMENTAL INVESTIGATION

CHAPTER XVI

THE DISPENSABILITY OF THE SYMPATHETIC NERVOUS SYSTEM[1]

ROBERT M. MOORE, M.D.

THE purpose of this paper is to review the conclusions which have been drawn from a series of experiments in sympathectomy, conducted in the Department of Physiology of the Harvard Medical School during the past few years. A detailed report of this work has been made by Cannon, Newton, Bright, Menkin and Moore (5).

During the course of experiments in cardiac denervation it was found that considerable portions of the sympathetic division of the autonomic nervous system could be removed from the cat with no apparent ill results (4). This led to an attempt to remove the entire sympathetic system in the hope that thereby more light might be thrown upon its functions, and complete sympathectomy has been successfully done in a number of instances.

TECHNIQUE OF SYMPATHECTOMY

During the earlier part of the work the technical procedure consisted of repeated operations, at each of which bilateral removal of a section of the sympathetic nervous system several inches in length was practised. Thus, in three or four stages, both trunks were removed from above the superior cervical ganglia to the level of the united ganglia just below the pelvic brim. This of course included section of all the splanchnic nerves and often the semilunar ganglia were removed as an additional measure. By this method it was found that cicatrization rendered it difficult to determine the exact extent of the preceding dissection. Another method is therefore now used which consists of the complete resection of one entire chain in one piece at one sitting. This is accomplished through three successive openings, one in the fifth and one in the ninth thoracic interspace, and the third in the abdominal midline. The thoracic trunk is dissected

[1] From the Laboratories of Physiology, Harvard Medical School.

free, from above downward, and is drawn through the diaphragm into the abdomen; the splanchnic nerves are severed and the abdominal chain is resected well into the pelvis; the entire chain is then delivered, intact, through the abdominal incision. The procedure requires from sixty to seventy minutes. The postoperative course is uneventful if proper attention has been paid to avoid sepsis and trauma. After two or three weeks the other trunk is removed in like manner. In the cat this method has repeatedly proven successful. When complete sympathectomy is done in the dog or in the monkey the dissection is interrupted at the diaphragm and the two abdominal chains are removed at a third sitting. In a number of instances the upper extent of the operation has been limited to the stellate ganglia. The cervical sympathetic nerve, although *in situ*, is isolated from the central nervous system and cannot be reflexly excited.

EFFECTS OF SYMPATHECTOMY

Cats from which one entire sympathetic chain has been removed, certainly show no very striking effects. The nictitating membrane is extended, and the pupil of the eye on the affected side, is narrower than its fellow when the animal is at rest. There is a paralysis of the hair-erecting muscles on the sympathectomized side. When the animal becomes excited there is reflex stimulation by way of the contralateral splanchnic nerve, leading to a secretion of adrenin which, despite the sympathectomy, causes a dilatation of the ipsolateral pupil and erection of the denervated hairs. If the contralateral adrenal gland is removed or denervated, excitement causes no erection of hair on the sympathectomized side and only that modicum of mydriasis which arises from the reflex inhibition of parasympathetic oculomotor tone. Wright and Harris (13), in unilateral sympathectomy experiments, found that there was an immediate rise of 1.6° to 2.8°C. in the skin-temperature of the sympathectomized extremity over its normal fellow and that this rise in skin-temperature persisted virtually undiminished for at least four months. In the writer's work he has noted that the peripheral vasodilatation is often so marked as to cause a severe congestion of the nasal passages on the side operated upon and to lead to a very profuse and troublesome discharge from that nostril. Except for these local changes, unilateral sympathectomy seems to be an entirely harmless procedure.

Bilaterally or completely sympathectomized cats have lived in the laboratory for more than a year. They show no evidences of ill

health. They eat well and usually gain weight. They like to be petted and behave in most ways as do normal cats.

Sympathectomized animals have difficulty in combating cold. Reflex hair-erection and reflex peripheral vasoconstriction are lacking. Such cats exhibit a marked antipathy to cold air and to drafts. It is not uncommon to see one literally live on a radiator during the winter months, descending from its perch only at feeding-times. When placed in a refrigerator at a temperature of 4° C., a sympathectomized cat shows a rapid decline in body-temperature which may amount to a fall of 2° C. within an hour. Violent shivering starts within ten to fifteen minutes and is usually effective in re-establishing the normal temperature. A normal cat may show no appreciable fall in body-temperature even after two hours and violent shivering does not usually set in until after one hour.

The basal metabolism has been determined in cats before and after complete sympathectomy. Sympathectomy produces no significant change in the total metabolism. Moreover, protein still exerts its specific dynamic action. Nakayama (8) has reported that following bilateral splanchnotomy both proteins and carbohydrates exert a greater specific dynamic action than when the splanchnics are intact. The author has observed no change in the specific dynamic action of foodstuffs following complete sympathectomy.

Meltzer (6), in 1920, advanced the hypothesis that the superior cervical ganglia of the rabbit and of the cat are necessary to life. Montgomery (7), in 1923, reported that rabbits, cats and rats quite regularly survived after bilateral superior cervical gangliectomy. The widespread practice of the Jonnesco operation[2] indicates that the superior cervical ganglia in man are certainly not necessary to life. The writer has seen severe and perhaps fatal symptoms arise in the cat following bilateral cervical sympathectomy when both chains were interrupted at one sitting. There follows, secondary to the vascular paralysis, an extreme congestion of the nasal mucosa, with a heavy exudate. The animal of necessity breathes through its mouth and this probably predisposes it to pulmonary infection. Moreover, three days after bilateral superior cervical gangliectomy in the rabbit, Underhill and Pack (12) have observed temperatures as much as 4° to 7°C. subnormal. It is very likely that in the cat also mouth-breathing leads to faster dissipation of body-heat. That these untoward effects of bilateral cervical sympathectomy are second-

[2] This volume, pp. 725, 782, 786 and 796.

ary to the vasodilatation, is shown by the fact that if the two cervical chains are severed separately, at an eight- to ten-day interval, no such serious results follow. It seems probable that by the time of the second operation sufficient peripheral tone is developed in the vessels of the side first denervated to enable the animal to "carry on" without serious disturbance in its heat-economy.

None of the author's observations would indicate that any part of the sympathetic nervous system is necessary to life. Spadolini (10, 11) reports that following section of the mesenteric nerves of the cat a severe depression ensues, with death in from three to eight days. He finds the notable postmortem lesion to be a necrosis and sloughing of the intestinal mucosa. He concludes that the mesenteric nerves exert a trophic influence upon the intestine. Although the author has destroyed the abdominal sympathetic innervation in over one hundred cats he has never seen troublesome symptoms arise which could be ascribed to this procedure. The completely sympathectomized cats eat heartily and gain weight. Bowel-action seems to be normal. It is difficult therefore to understand the cause of the phenomena which Spadolini describes. It is interesting, however, to note that the changes he ascribes to nerve-section are identical to those produced by an interference with the blood-supply to the intestine.

The writer has seen no indication that the sympathetic nervous system exerts any important influence upon the fundamental functions of growth, development, and reproduction. One entire sympathetic chain was removed in kittens from six to eight weeks old. These unilaterally sympathectomized kittens grow rapidly and are very active. Their gait is normal and they show no signs of muscle weakness or of muscle-atrophy on the sympathectomized side. One of these kittens died from a respiratory infection at four months after unilateral sympathectomy, and one at five months. Each had doubled its weight since operation. In neither could any difference be detected at autopsy between the sympathectomized extremities and their normal mates. The distribution of fat was identical. The total weights of the two forelimbs were equal. The two femurs and the two humeri were of the same dimensions and of the same weight. There was no significant difference either as to size or as to weight between the right and left thyroid glands, the right and left adrenal glands, or the right and left kidneys. Wright and Harris (13) have observed no difference in the growth of the long bones of the sym-

pathectomized extremities of kittens compared with their normal fellows after four months. In 1901 Saalfeld (9) reported that the hair of the cat grew more rapidly after sympathectomy but thought this was only a secondary effect, explaining it on the basis of improved nutrition as a consequence of the hyperemia. There is apparently, however, no good evidence to support the view that the sympathetic nervous system plays an important part in the growth or in the development of the organism.

No evidence is at hand of the ability of the male cat to take part in reproduction after sympathectomy, but one of the sympathectomized female cats gave birth to two kittens, conceived when the splanchnics were the only sympathetic nerves remaining and born six weeks after the splanchnics had been removed. One kitten had to be killed on account of postpartum injury; the other developed until independent and appeared to be entirely normal.

In relation to the hypothetical vagotonic and sympathicotonic states, the conditions of so-called autonomic imbalance, the experience of the author has been that completely sympathectomized animals, which should certainly represent conditions of relative vagotonia, live, thrive, and apparently enjoy all good health. True enough, the pupils are constricted, the heart-rate is slow, the arterial blood-pressure is somewhat diminished. But the heart does not beat as slowly as it does in the animal deprived of both vagus and sympathetic action, and the blood-pressure is still sufficiently high to maintain an efficient circulation under ordinary conditions. Digestive movements progress without diarrhea or other signs of hypermotility, and the sphincters open and close much as in the normal animal. In sum and substance, pathological symptoms are striking because of their absence.

Abel (1) has maintained that the chromaffin system is necessary to life. The author has seen animals survive indefinitely after removal of all sympathetic ganglia, excision of one adrenal, and ablation of the medulla of the other adrenal. It cannot be said that such an animal is entirely chromaffinless. Surely only a small remnant of its chromophil tissue remains, however, and were that system a vital one, symptoms of some severity should be expected to intervene.

Some years ago Dr. Cannon (2, 3) called attention to the fact that the sympathetic division of the autonomic nervous system, and the chromophil or medullary portion of the adrenal gland, are thrown into activity at those times of stress when the struggle of the organism

against the malevolent influences of the environment is most intense. Fear, rage, pain, exposure to cold are examples of conditions associated with sympathico-adrenal activity. The physiological changes which are brought about by the activity of this conjoint system are changes which are beneficial to the organism when it is operating under the tension of combat, of flight, of pursuit. The heart is accelerated and the arterial pressure is elevated. The intestines are relaxed and the vasoconstriction of the splanchnic field increases the blood-supply to the laboring muscles. The blood-sugar is elevated to supply a readily available source of energy to the muscles. The dilatation of the bronchioles facilitates the to-and-fro movement of air in the extra respiration, which maintains a high oxygen tension in the lungs and increases the oxygenation of the blood in the pulmonary capillaries. Through constriction of the spleen, stored red blood-corpuscles are poured out to aid in carrying this oxygen to the muscles. The secreted adrenin postpones fatigue, re-enforces the nervous cardiac acceleration, shortens the coagulation time of the blood. The picture is that of a diffuse and primitive mechanism, operating in a beneficial though extravagant manner, at a time when the conservation of stores and the economical expenditure of energy fade to a place of secondary importance in the event of the crucial moment when existence itself is at stake.

It has been seen that the sympathetic nervous system is not necessary to life. It has been concluded that it has no paramount importance in the daily round of the functions of digestion, assimilation, growth, development, reproduction. In what regard, then, is the sympathetic of great importance?

When a sympathectomized cat becomes emotionally excited, as when approached by a barking dog, it shows all the external signs of aggressive feeling except the erection of the hairs and the maximal dilatation of the pupils. The internal automatic changes which accompany excitement, however, are absent. There is no increase of adrenin secretion; there is no rise in blood-sugar; neither the polycythemia nor the lymphocytosis of emotional states appears. Reflex splanchnic vasoconstriction is lacking and the heart is accelerated only to that moderate degree produced by inhibition of vagal tone. Consequently blood-pressure changes are not great. There is no great shifting of the circulation to benefit the contracting muscles, no adequate provision of extra carbohydrate or of extra oxygen for them

to utilize, no secretion of adrenin to offset fatigue. It is extremely doubtful whether such an animal can defend itself with the efficiency and the endurance of the normal animal, in which these beneficial changes do occur. Here, then, lies the importance of the sympathetic nervous system. It is not only possible but very probable that the same animals which have survived so long and so well in the shelter of the laboratory would have succumbed in the struggle for existence if thrown out to fare for themselves in the alleyways.

DISCUSSION

The following questions submitted to Dr. Moore before the Commission, together with the answers to them, are here reported verbatim.

Dr. Timme: I suppose that the natural comment on this paper would be that we can congratulate ourselves that it was not the first one on the program. We might have had to adjourn after it. At any rate, I may say this: that I saw some of these cats in Dr. Cannon's laboratory some time ago and it is quite astounding to note what little effect, really apparent effect, such a widespread deprivation can cause, provided, of course, that the environment has not been changed to an anxious one.

Are there any questions? Dr. Weed was going to say a few words on this subject.

Dr. Weed: All I care to say is that it seems to me an extremely good presentation and a very great piece of work.

Dr. Jelliffe: I notice that in reading the paper the words were used, "This was not a complete sympathectomy," and that the cats were "apparently healthy."

Is it not pertinent to ask: (*a*) Was there not enough sympathetic nervous system left to allow the cat to function as it did? And (*b*), What would the cat have to say when asked about his health? (Laughter)

Dr. Moore: The cats seemed to be very happy about the whole matter. (Laughter)

Dr. Cannon: I am interested in this question that Dr. Jelliffe has asked and I should like to ask, in return: Where else is the sympathetic system than in this chain from the superior cervical ganglion down to the pelvis on each side of the central line?

Dr. Jelliffe: I can only reply to Dr. Cannon in somewhat his own phraseology, namely: That the sympathetic nervous system in its primordial, primary development is a non-synaptic syncytium distributed throughout the entire body, and if it

is a non-synaptic syncytium distributed throughout the entire body, only those parts which are in central connection with the spinal cord and with some of the higher centres have been severed. Furthermore, one of the notes that it seemed to me Dr. Forbes spoke of, showed that you did not sever any of the blood-vessels, and we have already seen some very interesting illustrations on the slide showing how widespread the syncytium of the vegetative nervous system is throughout the blood-vessels. So that through all the connecting blood-vessels there still remains an enormous amount of the vegetative nervous system.

Dr. Cannon: I will challenge Dr. Jelliffe to find anywhere in any publication of mine where I say that the sympathetic nervous system is a non-synaptic syncytium spread throughout the body.

Dr. Jelliffe: I did not read it in any publication of yours, but I did read it last night in a book referring to your work. (See Marston, W. M.: Emotions of normal people. New York, Harcourt, Brace and Co., 1928, p. 74. Later reported to me by Marston as "his inference" as basis for this comment.)

Dr. Cannon: I challenge anyone to cite the place where I say that. I know better than that. There is very good evidence that that is not true and that there are, in fact, synapses between the preganglionic neurones which have their cell-bodies in the brain and spinal cord——

Dr. Jelliffe: I was not speaking of the highly developed part of the vegetative nervous system, but of the primordial situation.

Dr. Cannon:—and the outlying neurones whose cell-bodies are in the peripheral ganglia; and that these postganglionic fibers are distributed to blood-vessels, glands, to smooth muscles generally throughout the body; and that if the ganglia which contain the cell-bodies of the postganglionic fibers are removed, necessarily the fibers which have their nutritive centres in these ganglia must degenerate throughout the body. If anyone here, any histologist, wants to challenge that remark, I wish he would do so now, because I shall learn something if he challenges it successfully.

Dr. Huber: Mr. Chairman, it is not my purpose to quarrel with Dr. Cannon, even in a friendly way. I happen to have seen the late Professor Langley demonstrate by experimental methods, at the Physiological Congress in Bern, in 1895, the innervation of the pilomotor muscles in the cat. The demonstration interested me very much, and my special attention to the sympathetic nervous system dates from that time.

It seems to me that in a sense Dr. Jelliffe is correct, but only in a limited sense. As I understand it, Dr. Cannon does not for one moment mean to state that he has removed the craniosacral sympathetic system. The thoracicolumbar division of the sympathetic system, with the cervical and other chain ganglia, has been removed. The ciliary ganglion, other head-ganglia and the entire vagus complex were left intact as were also the myenteric and submucal intestinal plexuses, the

vesicle ganglia and the ganglia about the pancreas. Nevertheless, this experiment is a remarkable one. It has impressed me as did the work of Langley in 1895.

It seems to me that we should earnestly and understandingly begin to study the sympathetic nervous system as a whole. I sincerely think the time is not distant when we shall be able to speak in terms of neurone-chains with reference to diencephalic connections and control of the sympathetic system. To what extent the visceral system is under the control of the cortex, I am not prepared to say.

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CHAPTER XVII

THE PARASYMPATHETIC CONTROL OF MUSCLE-TONUS[1]

S. W. RANSON, M.D.

INTRODUCTION

ORTHODOX physiology does not satisfactorily account for normal muscle-tonus nor for the various types of hypertonus and contracture. The inadequacy of the explanations of these phenomena, which can be deduced from the conception of a single motor innervation and the all-or-none law, has lead to the formulation of theories of dual innervation and a special holding mechanism. The theory which has attracted most attention is that skeletal muscle receives a tonic innervation from the sympathetic nervous system. But quite recently another theory was formulated by Frank (13, 14), namely, that tonic impulses are conveyed to the muscles antidromically over parasympathetic fibers in the dorsal roots. At the time this ingenious idea was conceived it had much in its favor. The pseudomotor phenomenon, a slow tonic contraction produced by the stimulation of the dorsal roots after the degeneration of the ventral root fibers, is closely allied to antidromic vasodilatation and to the contracture produced by acetylcholine, which is a powerful parasympathetic stimulant. And it is generally believed that section of the dorsal roots not only abolishes normal muscle-tonus but prevents the development of rigidity after decerebration and after the injection of tetanus toxin. When the author's attention was directed to the idea some five years ago it seemed to him to offer a solution to the tonus problem. Since that time the author and his associates have been engaged in putting the hypothesis to the test in a variety of experiments. Although considerable data bearing on the problem has been accumulated, no convincing evidence has been found in favor of Frank's hypothesis.

[1] From the Institute of Neurology, Northwestern University Medical School, Chicago.

PSEUDOMOTOR PHENOMENA

Under certain conditions, muscles can be made to undergo a slow tonic contraction by the stimulation of what are apparently sensory fibers. Examples are the Vulpian-Heidenhain contraction of the tongue and the pseudomotor phenomenon in the limb-muscles. In 1863 Vulpian and Philippeaux (66) showed that after section and degeneration of the hypoglossal nerve the tongue could be made to contract by the stimulation of the lingual nerve. This was due to the stimulation of the chorda tympani fibers; and stimulation of the lingual nerve above its junction with the chorda was without effect. Heidenhain (20) confirmed these findings and showed that the reaction reached its height about one week after the section of the hypoglossal nerve and remained at its maximum until the end of the third week when it began to decrease. The contraction caused the tongue to deviate toward the side of stimulation. The threshold was high and only stimuli much stronger than those necessary to activate a motor nerve like the hypoglossal, were effective. The contraction differed from that produced in the normal tongue by the stimulation of the hypoglossal nerve in that the latent time was very much greater and the response was slow and sustained. Single induction shocks were without effect or produced only a slight localized fibrillary twitching. Rapidly repeated strong induction shocks were required to produce any appreciable results.

In 1894 Sherrington (58) obtained a similar response in the limb-muscles by stimulating their sensory fibers several weeks after they had been deprived of their motor innervation. He cut the motor and sensory roots of the sixth and seventh lumbar, first and second sacral nerves proximal to the spinal ganglia and forty-two days later he stimulated the peroneal nerve with strong induction shocks. There occurred a slow dorsal flexion of the ankle and an extension of the toes. The contraction was slow in developing and persisted for several seconds after the cessation of the stimulus. Since the response did not occur if the roots had been cut on the distal instead of on the proximal side of the spinal ganglia, he concluded that the fibers concerned had their cells of origin in the spinal ganglia. The possibility that the contraction was due to the escape of electrical current along the nerve to the muscle, was ruled out by the fact that it occurred when the electrodes were located at a point on the nerve 20 cm. from the muscle.

These pseudomotor phenomena are not caused by the stimulation of the sympathetic fibers contained in the nerves. Van Rijnberk (54, 55) found that after degenerative section of the hypoglossal nerve, the stimulation of the cervical sympathetic trunk produced no effect on the tongue. This independence of sympathetic fibers also holds for the pseudomotor phenomenon in the limb-muscles. Van Rijnberk found that after the section of the spinal nerve-roots the stimulation of the abdominal sympathetic nerves caused no response in the muscle.

What Fibers Must Be Cut in Order to Prepare the Muscle for Pseudomotor Reactions?

It is clear from van Rijnberk's work that sympathetic fibers are not concerned in any way in these reactions. In all the earlier work on the pseudomotor reaction in the limb-muscles the motor and sensory roots were both cut proximal to the spinal ganglia. Van Rijnberk thought that if the motor roots alone were cut the reaction could not be obtained. This was interpreted as evidence that fibers, capable of inhibiting the response, leave the spinal cord over the dorsal roots and must be cut and degenerated before the reaction can be obtained. But Hinsey and Gasser (23) have been able to obtain the pseudomotor phenomenon in the cat's leg after section of the motor roots alone. This eliminates the necessity for postulating the existence of these inhibitory fibers in the dorsal roots. It would therefore appear that degeneration of the motor fibers is in itself sufficient to sensitize the muscles.

What Are the Fibers, the Stimulation of Which Causes the Pseudomotor Phenomenon?

The chorda tympani is of such a mixture that an answer to this question could scarcely be obtained by studying the Vulpian-Heidenhain phenomenon. In the case of the limb-muscles the problem is approaching solution. The degenerated motor fibers necessary for sensitization rule out the ventral root. Van Rijnberk has eliminated the sympathetic fibers. There remain only the fibers of dorsal root origin; and Sherrington has shown that the fibers which are responsible for the phenomenon have their cells of origin in the spinal ganglia. In the dorsal roots there are found myelinated fibers of all

sizes and many that are unmyelinated. Sherrington thought that the large myelinated fibers going to the muscle-spindles might be responsible for the pseudomotor phenomenon and that the responses were due to the contraction of the intrafusal muscle-fibers. But it does not seem probable that the few intrafusal fibers, widely separated as they are through the belly of the muscle, could produce the tensions up to 1 kilo which Hinsey and Gasser obtained from the cat's gastrocnemius. Furthermore, the proprioceptive fibers are all large or medium-sized fibers and there is good reason to believe that the fibers which cause the contraction are small.

Hinsey and Gasser (23) have called attention to the fact that the high threshold of stimulation of the fibers responsible for the pseudomotor phenomenon is convincing evidence that these fibers are small. They have investigated this question with the aid of the cathode-ray oscillograph. With this delicate instrument they were able to show that rapidly repeated stimuli of a strength sufficient to activate all the large and medium-sized fibers, as evidenced by the record of their action-potentials given by the oscillograph, did not cause the contraction. Only when the strength of the induction shocks was raised sufficiently high to bring the small fibers into action did the contraction occur. The effective stimuli were of about the same strength as those required to produce vasodilatation, and they were definitely shown to range in size from 3 to 5 μ (24).

It is known that the dorsal roots contain many small myelinated and unmyelinated fibers (Ranson (45)), but Hinsey (21) was unable to trace any of these to endings in the muscle-fibers. They could be traced along the blood-vessels and occasionally were seen in the intramuscular connective tissue very close to muscle-fibers. If it be true that they do not end on muscle-fibers, then the contraction produced by their stimulation must be pseudomotor as suggested by Heidenhain (3).

Relation of the Pseudomotor Phenomenon to Vasodilatation

It has been suggested that the response might be due to vasodilatation, since the nerves which produce the pseudomotor reaction also cause vasodilatation and since both these responses have a high threshold of stimulation and a long latency. But Heidenhain demonstrated that the movement was not due to the engorgement of dilated vessels with blood because the movement occurred in an excised tongue.

There is, however, a close association between the pseudomotor phenomenon and vasodilatation. Acetylcholine and nicotine (injected intra-arterially) are both powerful vasodilators (Ranson and Wightman (52)) and they both cause a contracture of denervated muscle very similar to the pseudomotor reaction. But there are some vasodilator drugs like histamine (18) which do not cause a shortening of denervated muscle. This very close relationship between vasodilatation and the pseudomotor phenomenon raises the question: In what way could vasodilator fibers on the vessels bring about the contraction? It is very improbable that the muscle-fibers are stimulated by the action-potentials of the sensory nerve-fibers in their neighborhood, as suggested by Langworthy (36, 37), because, if this were the case, one would expect to obtain the response from the large sensory fibers which have much greater action-potentials than do the small fibers; and it is known that these large fibers are not effective. Hinsey and Gasser (23) have suggested another possible explanation: "If the vasodilatation itself should take place according to Loewi's (41) humoral transmission theory, it is conceivable that the intermediate substance might also be pharmacodynamically active on skeletal muscle sensitized by denervation, although not so on a normal muscle."

In favor of this humoral transmission theory is the fact that the action-current in the pseudomotor phenomenon is wave-free. In a nerve-muscle tetanus a record of the action-currents shows waves corresponding in period to the stimuli. Schäffer and Licht (57) found that the pseudomotor phenomenon and acetylcholine contracture in the tongue are both accompanied by the same electrical change, namely a large monophasic variation, as recorded by the string galvanometer. The record of the pseudomotor phenomenon was as free from waves as the drug contracture. Hinsey and Gasser (24) have examined the pseudomotor phenomenon in the limb-muscles with the cathode-ray oscillograph and showed that during contracture no waves of potential appeared corresponding to the stimuli.

This smooth, waveless action-current is additional evidence against the idea that the pseudomotor phenomenon is brought about by the direct stimulation of muscle by nerve-fibers. If the contraction were brought about by accessory endings of the dorsal root-fibers on muscle-fibers or by the escape of the action-potentials of sensory fibers, the action-current should show waves corresponding in phase to the stimuli applied to the nerve; but if the action is an indirect one, the absence of these waves could be understood.

Relation of the Pseudomotor Phenomenon to the Drug Contractures

When isolated frog-muscle is immersed in a solution containing a small amount of nicotine a tonic shortening is induced. Langley (35) has shown that the nicotine acts just as well after nerve-section. Hence it acts beyond the nerve-ending in what he calls the neural region of the muscle, the receptive substance of Langley. Acetylcholine acts in a similar way. Riesser and Neuschlosz (53) state that the prolonged shortening of the frog's gastrocnemius caused by both of these drugs is due to a stimulation of Langley's receptive substance and is prevented by curari, atropine and novocaine. Furthermore, when injected into the blood-stream, nicotine and acetylcholine cause a slow and rather prolonged shortening of denervated mammalian muscle. Since acetylcholine is a powerful parasympathetic stimulant, Frank, Nothmann and Hirsch-Kauffmann (15–17) have considered its action as evidence of the existence of a special parasympathetic innervation. But Gasser and Dale (18) find that the facts when critically considered do not support such a conclusion.

The author has already called attention to the fact that the action-current of the pseudomotor phenomenon, like that of the acetylcholine contracture, is wave-free. Another point of similarity between the acetylcholine contracture and the pseudomotor phenomenon is that both are inhibited by adrenalin (Hinsey and Gasser (23)). Acetylcholine being a parasympathetic stimulant and adrenalin, which inhibits both, being a sympathetic stimulant, one could argue that both were parasympathetic phenomena. Frank, Nothmann and Hirsch-Kauffmann (15–17) found that acetylcholine contracture was antagonized by large doses of scopolamine (up to 15 mg.). Hinsey (25) was able to inject 2 mg. of scopolamine hydrobromide without causing any considerable decrease in the response to acetylcholine and without any effect whatever on the pseudomotor phenomenon. This dose is far in excess of that required to block any known parasympathetic responses. This very large dose of scopolamine was injected intra-arterially in such a manner that it was all carried with the blood-stream into the leg whose reactions were to be tested. Hinsey also found that 2 mg. of atropine were ineffective in blocking the pseudomotor phenomenon.

Gasser and Dale (18) point out that acetylcholine, in addition to its power to reproduce parasympathetic effects in involuntary muscle, has the ability to imitate the action of nicotine on ganglion-cells.

They present reasons for believing that the contracture which it produces on denervated muscle is due to its nicotine-like action, rather than to its efficacy as a parasympathetic stimulant.

The Effect of Parasympathetic Drugs on Muscle-Tonus

In this connection it should not be overlooked that both atropine and scopolamine tend to decrease the hypertonus in paralysis agitans and in the postencephalitic Parkinsonian syndrome. According to Marinesco and Nicolesco (42) the rigid muscles become softer, the cogwheel phenomenon diminishes, passive movements become easier, and the tendon-reflexes become more lively. This has been interpreted by Kuré and Shinosaki (33) as due to the paralyzing action of these drugs on hypothetical parasympathetic fibers ending in skeletal muscle. Schäffer (56) has shown that Tiegel's contracture is exaggerated by parasympathetic stimulants (physostigmine and pilocarpine) and inhibited by atropine and adrenalin. No satisfactory explanation has yet been given of the effect which these drugs appear to have on these states of abnormally increased tonus.

Huggett and Mellanby (27) injected 2 mg. of atropine intravenously without affecting muscle tonus either in the intact anesthetized cat or in the decerebrate preparation. A similar absence of effect was observed after the intravenous injection of pilocarpine. It will be seen that the pharmacological evidence of the existence of parasympathetic tonus-fibers supplying skeletal muscle, is far from convincing. The well-established facts are not easily harmonized with one another. One can only say that at present no satisfactory explanation can be given of the action which various parasympathetic stimulant and depressant drugs have on skeletal muscle.

THE RÔLE OF THE DORSAL ROOTS IN MUSCLE-TONUS

Quite recently Frank (13, 14) formulated the theory that tonic impulses are conveyed to the muscles antidromically over parasympathetic fibers in the dorsal root. This theory received considerable attention because it has been believed since the time of Brondgeest (5) that the section of the dorsal roots causes a loss of tonus in the muscles supplied by the divided roots. The conception of tonus as a proprioceptive reflex has been extensively elaborated by Sherrington (59, 60) and his associates. But most of the observations reported

by these workers could as easily be explained by Frank's hypothesis (13, 14) as by the proprioceptive reflex theory.

The most direct approach to this problem is to cut the dorsal roots and to note the effect on tonus. If either Frank's hypothesis or the proprioceptive reflex theory is correct, one would expect marked and persistent atonia to result from such an operation; and it is generally believed that this is the case. That this belief is to a certain extent erroneous has been shown by a study which the author (48) recently made of the rôle of the dorsal roots in muscle-tonus. The literature was there reviewed in some detail. Here it need only be said that Trendelenburg (65) cut the dorsal roots supplying the wings in pigeons without altering the tonus of the wing-musculature. Bickel (2), Mott and Sherrington (43) and Kopczýnski (29) seem to have obtained hypertonia and contracture in the de-afferented limbs of some of their animals. Liljestrand and Magnus (40) found that during the first few days after the section of the dorsal roots of one brachial plexus, the triceps was entirely flaccid but that it retained the capacity for active movement. After about one week the muscle again acquired tonus and this increased with time. Foerster (10) advocated cutting the dorsal roots as a cure for spastic paralysis; but the operation has not been very successful (Steinke (63)).

Hypertonia after Section of the Dorsal Root

In the author's experiments (48) on cats, when one hind-leg had been completely de-afferented by the section of the dorsal roots close to the spinal cord, that leg became atonic for only about twenty-four hours. Subsequently an overaction of the extensor muscles nearly always developed and usually also an increased resistance to passive flexion. After from two to four weeks these evidences of hypertonia largely disappeared. During the period of hypertonia the de-afferented leg was adducted and extended and was quite useless. Later, when the cat was again able to walk, it had difficulty in flexing this leg, which tended to be dragged with the dorsal side of the foot down. This inability to use the limb gave the appearance of a paresis. Contracture, a permanent shortening of the extensor muscles which persists after the section of the motor nerves or even after the death of the animal, not infrequently developed in muscles de-afferented by the section of the dorsal roots proximal to the spinal ganglia. For some reason not easily understood, the removal of the spinal ganglia

delayed or prevented the development of the hypertonia and contracture in the de-afferented muscles.

Decerebrate Rigidity

This condition is one of heightened tonus in the antigravity muscles, especially in the extensor muscles of the limbs, caused by transection of the mesencephalon. To the extent that this heightened tonus is maintained by impulses travelling out over the dorsal roots it should be decreased or abolished by dorsal root section. The author has found (48), in agreement with Sherrington, that the section of the dorsal roots in a decerebrate cat caused the immediate disappearance of the rigidity. But this must be attributed at least in part to shock. If after the section of the dorsal roots an animal was allowed to recover for several weeks before decerebration, decerebrate rigidity was slow to develop. But after a lapse of time, varying from thirty minutes to several hours, a tremulous oscillating type of rigidity developed. This is contrary to the findings of Sherrington (59, 60) but in agreement with Liljestrand and Magnus (40). The last-mentioned authors found that a certain amount of rigidity developed in de-afferented muscles after decerebration. Pollock (44), in experiments conducted in collaboration with Davis, also obtained decerebrate rigidity in de-afferented muscles.

The Crossed Extensor Reflex

Another phenomenon, offering an opportunity to test the significance for tonus of dorsal roots and of any parasympathetic fibers which they may contain, is the crossed extensor reflex. The response has been studied chiefly in decerebrate and in spinal preparations. Normal waking cats do not show this reflex. But even in waking cats the author has found (48) the reflex well developed in de-afferented limbs. Pinching the toes of the normal leg caused the opposite de-afferented leg to be thrust out promptly in extension. In most cases the cat, though fully awake, could not inhibit this reflex and the limb remained in full extension as long as the stimulus was applied. The response was steady and persistent and appeared to outlive the stimulus by an appreciable period. It imposed on the limb a definite posture and appeared to be as definitely tonic as are the labyrinthine and neck reflexes described by Magnus. It seemed desirable therefore to obtain tracings of these reflexes in decerebrate animals.

In describing the crossed extensor reflex in the decerebrate cat Sherrington ((59), p. 129) says: "The reflex contraction thus excited in the vastocrureus when that muscle has its own afferents intact is of considerable duration; the contraction rises deliberately to a maximum, which is maintained for some seconds and then slowly declines. But in the de-afferented preparation the course of the reflex contraction runs otherwise. It rushes to its maximum and then as quickly or almost as quickly subsides, presenting hardly a trace of the prolonged maintenance and slow decline characteristic of it in the decerebrate muscle still possessing afferents."

In cats decerebrated at the upper border of the mesencephalon these observations of Sherrington's have been confirmed (51). Under these conditions the crossed extensor reflex in normal muscle is maintained long after the stimulus ends but in de-afferented muscle it ceases abruptly on the cessation of the stimulus. If, however, the transection of the brain-stem is made at the upper border of the pons, there is little, if any, difference in the crossed extensor reflex as obtained fom normal and de-afferented muscle. After such low decerebrations typical tonic crossed extensor reflexes can be easily obtained from muscles whose hypothetical parasympathetic tonus-fibers have been cut in the dorsal roots. It seems probable that after high decerebrations a tonic inhibitory centre located in the upper part of the mesencephalon is responsible for the rapid relaxations of the crossed extensor reflexes obtained from de-afferented muscles. When this centre has been cut away in a low decerebration the crossed extensor reflex has essentially the same tonic character whether or not the muscle is de-afferented.

Labyrinthine Reflexes

Spiegel (62) found that dorsal root-section did not prevent the development of postural labyrinthine reflexes in the frog. The author (48) has found that tonic neck and labyrinthine reflexes, expressed as flexion or extension of the hind-legs and obtained by rotating the head first to one side and then to the other or by raising or lowering the head, were easily obtained in six out of eight decerebrated cats and were, without exception, brisker on the de-afferented than on the control side. In the cat, Pollock (44) has found, in experiments which were conducted in collaboration with Davis, that section of the posterior roots in a decerebrated cat does not sufficiently modify

the rigidity produced by labyrinthine reflexes to enable one to point out the differences between such rigidity and that in an animal with the posterior roots intact. This makes it clear that the integrity of the hypothetical parasympathetic fibers in the dorsal roots is not essential for the development of labyrinthine tonic reflexes.

Tetanus

Another condition in which there is a marked exaggeration of the tonus of the extensor muscles, is represented by tetanus. Liljestrand and Magnus (40) thought that dorsal root-section prevented the development of tetanus rigidity. Elsewhere the author (49) has reviewed the literature on this subject in some detail and has recorded experiments which show that, while under certain conditions the experiments of Liljestrand and Magnus can be repeated with similar results, it is not true that section of the dorsal roots prevents the development of tetanus rigidity. The onset of the rigidity as measured by the resistance to passive movement may be delayed by dorsal root-section. But tetanus rigidity and even contracture develops in de-afferented muscle. Rigidity and contracture develop even after degeneration of all of the sensory fibers has been brought about by the removal of the spinal ganglia. This rules out the possibility that the rigidity might be due to the action of the toxin on the spinal ganglion-cells and on the fibers arising from them and ending in the muscles. But it must be admitted that there is some evidence for a direct action of the toxin on the muscle-fibers.

Experiments with Nicotine

Some years ago the author (47) presented evidence in favor of Frank's hypothesis. In decerebrate cats the roots and spinal ganglia of one lumbosacral plexus were exposed and without opening the dura they were bathed in a solution of 0.04 per cent nicotine. This caused a marked decrease in the rigidity without decreasing the extent of the crossed extensor reflex obtained in each leg by pinching the toes of the opposite foot. In fact, this reflex was even brisker on the nicotinized side. This showed that the conductivity in the motor and sensory fibers was not noticeably impaired. The only explanation of these results which occurred to the author at that time was that the nicotine acted on the spinal ganglia, blocking synapses over which the tonic impulses from the dorsal roots had to pass in order to traverse

the spinal ganglia. Another explanation has been suggested by Forbes (11). Forbes and Olmstead (12) have presented evidence to show that in tonic contractions, such as the crossed extensor reflex, nerve-impulses travel down the motor fibers in such rapid succession that the fibers are in a relatively refractory state and a considerable percentage of the motor nerve-impulses, and probably a majority of them, are subnormal. These subnormal impulses are more readily stopped by an alcohol-block in the nerve than are normal full-sized impulses. It is possible that nicotine produces a similar block in the nerve, interrupting these rapidly repeated subnormal impulses but allowing the full-sized impulses to pass.

Stimulation of the Dorsal Roots

The question of the parasympathetic tonus-fibers in the dorsal roots may be approached in another way. These fibers, if present in the dorsal roots, must also be present in the peripheral nerves and should be brought into play when a motor nerve is stimulated. But a single induction shock applied to a motor nerve causes only a brief twitch. To produce the pseudomotor phenomenon, Hinsey and Gasser (24) had to apply strong and rapidly repeated stimuli to the sensory fibers remaining in the sciatic nerve after degenerative section of the ventral roots. If the same small fibers with high threshold that produced the pseudomotor phenomenon are concerned with tonus, they could be activated only by strong rapidly repeated stimuli. When a peripheral nerve, like the popliteal, is stimulated with strong rapidly repeated induction shocks for a period as long as the latency of the pseudomotor phenomenon, the resulting tetanus of the gastrocnemius goes over into a contracture which relaxes very slowly. This is what the physiologists call a fatigue-contracture. On the assumption that such a fatigue-contracture might be due to the activation of parasympathetic tonus-fibers in the mixed nerve, the author (50) applied similar stimuli to the seventh lumbar and first sacral ventral roots and recorded the contractions of the gastrocnemius. Prolonged stimulation of the ventral roots by strong faradic stimuli caused contracture in the gastrocnemius as readily as if the same stimuli had been applied to the mixed nerve. While no one has yet given a satisfactory explanation of this so-called fatigue-contracture, it cannot be attributed to the stimulation of parasympathetic tonus fibers of dorsal root origin.

At the Oxford meeting of the British Association for the Advancement of Science, Denny-Brown (8) presented the mechanical and electrical records which he had made with the precise recording apparatus in use in the physiological laboratory of Oxford University. He had been unable to find any difference in the records when the ventral roots alone were stimulated and when the stimulation was applied to the mixed nerve. This was advanced as evidence against the existence in the nerve of special tonus-fibers derived either from the dorsal roots or from the sympathetic nervous system.

HISTOLOGICAL EVIDENCE

Endings of Dorsal Root Fibers in Muscle

The idea that impulses, carried antidromically over parasympathetic fibers in the dorsal roots, are responsible for tonus at once raises the question as to what fibers of dorsal root origin actually end in muscles. If muscle possesses a double or, as Ken Kuré (34) maintains, a triple innervation, this should be susceptible of histological demonstration. Somatic motor-fibers ending in motor end-plates are easy to find but the case is otherwise in regard to the hypothetical sympathetic and parasympathetic endings. Other investigators will consider the vexed question of the sympathetic innervation of skeletal muscle. But the author must inquire whether parasympathetic fibers of dorsal root origin can be demonstrated as ending on skeletal muscle-fibers.

One can scarcely conceive of tonic impulses being conveyed antidromically over the sensory fibers which end in the muscle-spindles, because the muscle-spindles are not sufficiently numerous to account for the powerful tonic contractions or for the high tension developed by the gastrocnemius in the pseudomotor phenomenon. Other muscle-fibers must be involved. In addition to the spindles there are in skeletal muscles three other kinds of sensory end-organs—tendon-spindles, Pacinian corpuscles and free nerve-endings—all of which, since they are found in the connective-tissue framework and not directly on the muscle-fibers, may be excluded as possible factors in the antidromic conduction of tonic impulses. At one time we were inclined to consider the possibility that other fibers of dorsal root origin might end on muscle-fibers. Boeke (3) had apparently demonstrated the double innervation of skeletal muscle-fibers; and there were

some reasons for considering that the fine unmyelinated fibers, which he thought were sympathetic, were really of dorsal root origin, perhaps branches of the large fibers to the muscle-spindles and tendon-spindles. Kulchitsky's (30) studies of frog's muscle stained with methylene-blue offered some justification for such an interpretation. He demonstrated that there are in frog-muscle unmyelinated fibers which are branches of myelinated sensory fibers. These fine fibers end "in a bush of ramifying threads with leaf-like expansions at their ends." These endings rest directly upon the surface of the muscle. They are epilemmal and possess no granular sole-plate nor nuclei. They correspond to the grape-like sensory endings found in the extrinsic muscles of the mammalian eye by Huber (26), Crevatin (7) and Dogiel (9). In order to rule out the possibility that the unmyelinated fibers, which Boeke and Dusser de Barenne (4), Agduhr (1) and Kuntz and Kerper (31) found innervating mammalian skeletal muscle, were really of dorsal root origin, Hinsey began at the author's suggestion a thoroughgoing investigation of the innervation of the quadriceps muscle of the cat. He isolated in turn the motor, sensory and sympathetic fibers supplying the muscle. The sensory fibers were isolated by the degenerative section of the ventral roots and by the removal of the lumbar sympathetic chain. The sympathetic fibers were isolated by cutting the nerves distal to the spinal ganglia and proximal to the rami communicantes. The material was stained by the pyridine-silver technique, the adequacy of which was shown by the wealth of fine fibers which it stained on the intramuscular blood-vessels. Hinsey (21) was unable to demonstrate Boeke's accessory fibers and could find no evidence of any fibers of dorsal root origin ending in the muscle except those which terminated in muscle-spindles, tendon-spindles, Pacinian corpuscles and free nerve-endings in the connective-tissue. Some of these free sensory nerve-endings lay very close to muscle-fibers, but the number of such close approximations was so small that it is not possible to attach any functional significance to them.

Hinsey (22) also made a study of the innervation of the blood-vessels in those preparations in which the sensory and sympathetic fibers had been isolated. Fibers of dorsal root origin were observed in the adventitia of the small arteries and veins, arterioles and venules. While extending to the terminal arterioles they were not found on the capillaries. Hinsey gives a detailed survey of the literature on

the innervation of muscle and of blood-vessels. His work makes it clear that if antidromic impulses, conveyed over the dorsal roots, exert an influence on tonus it can only be by way of the blood-vessels. How this might come about has already been suggested in the first part of this paper.

Efferent Fibers in the Dorsal Roots

It is well known that there are efferent fibers in the dorsal roots of birds (Cajal (6), von Lenhossék (39) and van Gehuchten (19)) but their presence in mammals has never been satisfactorily demonstrated. We may pass over the older work of Joseph (28) and Singer and Münzer (61) to consider the recent paper of Ken Kuré and his associates (32). Nine to twelve weeks after the section of the dorsal roots proximal to the spinal ganglia Ken Kuré found many fine myelinated fibers in the central stumps of the divided roots. These were interpreted as parasympathetic fibers arising from cells in the posterior horn and ending in the spinal ganglia in synaptic relation to neurones whose fibers run out in the peripheral nerves. After section of the dorsal roots they found chromatolysis of cells in the base of the posterior horn. Chromatolysis of cells in the gray matter of the spinal cord as a result of dorsal root section has been seen by other observers—Warrington (67) and Lapinsky (38)—but it is quite possible that this is due to vascular disturbances resulting from section of the small arteries accompanying the roots. Ken Kuré's observation of myelinated fibers in the proximal stumps of the severed roots many weeks after the section cannot be considered as evidence because of the possibility of regeneration from the spinal ganglia which were left in place.

Timasheff (64) cut lumbar dorsal roots in dogs and, after the lapse of from three to fifteen days, studied the part of the roots still attached to the spinal ganglia in preparations stained by the Marchi and other methods. He found that about 5 per cent of the fibers underwent degeneration. There was chromatolysis in some of the cells of the corresponding segments of the spinal cord, chiefly in its gray matter, but also to some extent in that of the opposite side. Cells in all parts of the gray matter were involved but chiefly in the anterior and lateral parts of the anterior gray column. He concluded that there were a few centrifugal fibers in the dorsal roots. But the evidence is far from convincing.

In the course of other studies the author (46) had the opportunity to examine the proximal stumps of divided dorsal roots stained by the Pal-Weigert, Marchi and pyridine-silver methods. In none of these has he ever seen any clear-cut evidence of efferent dorsal root-fibers. The experiments are listed in Table V. In the first four of these experiments the lumbosacral dorsal roots were ligated proximal to the spinal ganglia; in the remaining six, they were cut. So far as could be determined from the Marchi preparations the fibers in the proximal stumps underwent degeneration. Obviously this does not exclude the possibility that fine myelinated or unmyelinated fibers may have remained normal and passed unnoticed in the Marchi preparations.

TABLE V

EXPERIMENTS ON THE STUMPS OF DIVIDED DORSAL ROOTS

ANIMAL NO.	ROOTS	OPERATION	DURATION	STAIN
			days	
1	L 6, 7, S 1	Ligated	24	Pyridine-silver
2	L 4, 5, 6	Ligated	24	Pyridine-silver
3	L 6, 7	Ligated	74	Pal-Weigert
4	L 5, 6, 7	Cut	74	Pyridine-silver
5	L 6, 7	Cut	24	Marchi
6	L 7, S 1	Cut	70	Pyridine-silver
7	L 7, S 1	Cut	54	Pal-Weigert
8	L 6, 7	Cut	20	Marchi
9	L 6, 7	Cut	14	Marchi
10	L 6, 7	Cut	51	Pyridine-silver

In the pyridine-silver preparations of Cats 1, 2, 3, 6, and 10, a varying small number of fine axones of normal appearance were seen entering the cord from the degenerated root. In Cats 3 and 7 a few fine myelinated fibers could also be seen in degenerated roots as they entered the cord. These fibers may have been efferent dorsal root fibers whose cell bodies were within the cord or they may have been regenerating fibers growing from the root into the cord. The spinal ganglia had not been removed and the time which had elapsed was sufficient for the appearance of regenerating fibers (twenty-four days for unmyelinated fibers and fifty-four days for myelinated fibers). The fibers were more abundant near the cut-end of the root and increased in number with the time which the animals survived the operation.

In Cats 1 and 2, twenty-four days after the roots had been tied, there were a moderate number of fine axones in the dorsal roots. These were more abundant near the cut end of the root than next the cord. They differed from the normal unmyelinated fibers chiefly in their irregular course and grouping. Some were branched, but end-bulbs, typical of regenerating fibers, were not seen. As has been said, only a few axones could be traced from the root into the cord. In Cat 4, seventy-four days after the operation, the proximal stumps of the divided dorsal roots were crowded with fine axones which resembled normal fibers. These were present in great numbers up to the point where neuroglia takes the place of connective-tissue just before the root enters the cord. Beyond this point only a few axones extended into the cord. Similar observations were made on Weigert preparations from Cats 6 and 10.

There can be no question but that the great numbers of fibers in the degenerated roots can be explained only on the basis of regeneration. But the possibility cannot be excluded that the fine fibers seen actually entering the cord may have had their cells of origin there. It is to be regretted that the spinal ganglia were not removed in these experiments so as to exclude the possibility of regeneration. Only by excluding this possibility can the question of efferent dorsal root fibers be settled.

SUMMARY

A review is given of the facts which bear on Frank's hypothesis (13, 14) that tonic impulses are conveyed to the muscles antidromically over parasympathetic fibers in the dorsal roots.

The pseudomotor phenomenon, caused by stimulating the sensory fibers after the motor fibers to a muscle have degenerated, has much in common with the contracture caused in the same denervated muscle by acetylcholine, which is a parasympathetic drug with a powerful vasodilator action. The relation of these phenomena to antidromic vasodilatation is discussed. Antidromic vasodilatation and the pseudomotor phenomenon are probably both brought about by the fine dorsal root fibers that accompany the blood-vessels. Although the pseudomotor phenomenon and acetylcholine contracture are inhibited by adrenalin, they are not inhibited by large doses of scopolamine and atropine. Hence the pharmacological evidence is against the reactions' falling definitely in the parasympathetic class. On the other hand,

the favorable action of atropine and scopolamine on the Parkinsonian rigidities must not be forgotten.

The importance of the dorsal roots for muscle-tonus has been overstated. Contrary to the usual belief, de-afferented muscle does not remain permanently atonic but recovers some of its tone and may for a time become hypertonic. Decerebrate rigidity, tonic crossed extensor reflexes and labyrinthine tonic reflexes can be obtained from de-afferented muscle. This shows that whatever rôle the dorsal roots may play in tonus, the fibers of the ventral roots are sufficient in themselves to produce tonic contractions.

No one has as yet succeeded in showing that stimulation of the dorsal root fibers concomitantly with the motor fibers alters the character of the contraction evoked by stimulation of the ventral root fibers alone.

There is no histological evidence that dorsal root fibers have any endings on the muscle-fibers in the limbs of mammals other than the endings in the muscle-spindles. Tendon-spindles, Pacinian corpuscles and free nerve-endings are found in the intramuscular connective tissue and cannot come into consideration in this connection. The branches of sensory fibers, which end in grape-like terminals on the surface of frog muscle-fibers and in the intrinsic muscles of the mammalian eye, appear to be absent from the limb-muscles of mammals. A histological demonstration of parasympathetic nerve-endings in the mammalian limb-muscles has not yet been given.

It remains an open question whether or not there are any efferent fibers in the dorsal roots; but even if these are absent the possibility of antidromic conduction over the sensory fibers, remains as postulated by Langley for vasodilatation.

DISCUSSION

The following questions submitted to Dr. Ranson before the Commission, together with the answers to them, are here reported verbatum.

Dr. Weed: I should like to say that I quite agree with what Dr. Ranson has said and am in sympathy with his conservatism. In one person's hands and with one person's technique such a simple thing as cutting the dorsal roots, proximal to the ganglion, may give one picture of the animal; and in another person's hands, another picture.

The reason for this difference is that in operating upon the nervous system in

a small mammal the element of trauma and the element of possible low-grade infection come in; and we may also have irritative phenomena, as well as phenomena of shock, following closely after the operation. These factors would give an entirely different group of symptoms in the animals from those in the original group.

For instance, many of these experiments that Dr. Ranson reported on the effect of cutting the ganglia, were repeated by Dr. Coman in the laboratory in Baltimore. Dr. Coman never saw any of the irritative phenomena, or what we call the irritative phenomena, such as hypertonus. The reactions in every case, where an essentially similar technique was used, were quite different from those reported by Dr. Ranson. I do not believe there is any real reason for this, except that different lesions are caused by different observers; and with the section of the dorsal roots, proximal to the ganglia, either one or both of these types of phenomena (hypotonus or hypertonus) may occur, following the operation.

Dr. Ranson: I am inclined to think that when the cord is exposed there is inevitable irritation. In the cat, the dura is so lacking in extent that it is impossible to suture it as is done in man. Therefore, in all of these experiments the cord is left exposed to the wound in the muscles. Some irritation probably enters, and perhaps is responsible for hypertonus.

The thing I should like to emphasize is that all observers who have studied the structure of the cord after such an operation have found chromatolysis in the cord-cells and more or less degeneration in the cord. That is inevitable. And when the muscle remains hypotonic, the possibility exists that the degeneration has been even more extensive than in those cases where hypertonus exists.

I should like very much to see sections of cords which had been operated upon, where the animals remained flaccid. Until someone shows sections of spinal cords operated upon in that way and shows that they have suffered less damage than the others, there remains in my mind the probability that greater damage accounts for the atony.

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CHAPTER XVIII

THE REGENERATION OF SYMPATHETIC NERVE-FIBERS[1]

FERDINAND C. LEE, M.D.

INTRODUCTION

THE sympathetic nerve-trunks, in contrast to the other peripheral nerves, have received relatively little study as regards their ability to regenerate. Several reasons for this difference can be advanced. In the first place, the sympathetic nerve-trunks are neither large nor easily accessible. Furthermore, they frequently are not independent but course as one trunk with other nerves, as is the case, for example, in the dog, where the cervical sympathetic and the vagus nerve form one trunk. Again, it is often difficult to test quantitatively the physiological action of a sympathetic nerve. Finally, the anatomy of these fibers, particularly of their terminations, is still a large field for investigation. Under such circumstances it is all the more remarkable that what little is known of the basic physiology of these fibers is in great part due to the efforts of one man, J. N. Langley (8), who had that rare gift of observation which enabled him to obtain much important data and draw many conclusions from the use of only a few animals. Even though little is known about the regeneration of these fibers, either anatomically or physiologically, the brevity with which this large subject is treated by Müller (9) in his excellent book on the sympathetic nervous system, hardly seems justified. The purpose of this article is to present some of the data collected during the year 1928 on the subject of sympathetic nerve regeneration.

MATERIAL AND METHODS

The cervical sympathetic chain was used exclusively for these experiments. This nerve-trunk was chosen because it was one of the easiest to dissect, and also because lesions in it could be readily observed in some of the peripheral organs, such as the eye. Of all the changes which took place after section of this nerve, the constriction

[1] From the Surgical Hunterian Laboratory, Johns Hopkins University.

of the pupil, the enophthalmos, the approximation of the eyelids, the protrusion of the nictitating membrane, and the rise in temperature of the skin of the affected region were the most outstanding. The congestion of the conjunctiva and the buccal membrane, the difference in the texture of the skin, the pilomotor effect, and the increase in pigmentation of the iris were other results of cervical sympathetic paralysis which were inconstant and did not lend themselves well to this study. In two animals a marked salivation occurred. At first the experiments were conducted on dogs, but soon the cat was found to be a much more suitable animal, since, in the neck, the cervical sympathetic chain could be separated easily from the vagus nerve, and because the pigmentation of the iris made measurements of the pupil less difficult. This report is based on the study of thirty-seven cats.

Under aseptic precautions the cervical sympathetic chain was cut across with a sharp scalpel about 2 cm. from the inferior pole of the superior cervical ganglion. The severed ends were then approximated with a single suture of China headed silk. In some cases the nerve-ends after section were in such good apposition that no suture was placed, especially because the vagus nerve acted as a splint. As a rule it was not difficult to distinguish between the two nerves, since the sympathetic nerve was smaller and more compact, and had a slightly bluish-gray color. Rarely was it necessary to resort to the use of the induction coil to establish absolutely the identity of the sympathetic nerve. In two cats the cervical sympathetic fibers coursed in two distinct trunks. In one animal a small ganglion was found about 1 cm. below the superior cervical ganglion. Langley (4) found such a ganglion in a few instances.

After operation the animal was studied with regard to three main conditions,—the diameter of the pupil, the prominence of the nictitating membrane, and the temperature of the ears. For the ordinary record the pupil was measured directly with the aid of a millimeter rule, with both eyes under the same intensity of illumination. A better record at crucial periods in the postoperative course was obtained by photography, using a flash powder and a fast lens. By this method the position of the nictitating membrane was also obtained. The temperature of the ears was measured by folding the ear around the bulb of a thermometer and maintaining this relationship with the aid of two large serrefines with weak grip and jaws covered

with pieces of a rubber bath sponge. The temperature of both ears was recorded simultaneously. Besides this method of recording temperature, thermocouples and a suspension galvanometer were employed, the thermocouples being placed in each auricle and the resulting difference of potential translated into degrees of temperature. With this apparatus differences of a hundredth of a degree centigrade could be readily detected. However, it must be added that this refined method of recording temperatures did not measure up to expectations when slight differences in temperature between the two ears were present, because the temperature of the normal ear always varied a little during the examination, and this fluctuation was greater than the sensitivity of the thermocouple. Rectal and room temperatures were also noted.

Frequently the operative site was exposed aseptically at various periods and the proximal nerve-trunk was stimulated with a weak induced current in order to determine whether any conduction extended through the anastomosis. Finally, before the nerve-trunk was removed for histological study, it was again stimulated.

Since the problem under discussion centred primarily in the axis-cylinders, the majority of the nerve-tissue was accordingly stained by a modified Bielchowsky stain described by Cuajunco (2). Since this stain has again been modified slightly in this work, it is given in detail.

Immerse tissue in 50 per cent neutral formalin for 48 hours. (Transfer to 10 per cent formalin for preservation if necessary.)

1. Wash in running water for 3 to 4 hours.
2. Wash in distilled water for 3 to 4 hours.
3. Immerse in pure pyridine at a temperature of 37°C. for 4 to 5 days.
4. Wash in distilled water until pyridine has been removed. Usually 3 to 5 hours are necessary.
5. Immerse in 3 per cent solution of silver nitrate for 4 days.
6. Wash in distilled water for 3 to 4 hours.
7. Reduce in ammoniacal silver solution (see below) for 24 hours.
8. Wash in distilled water for 4 hours.
9. Fix in 50 per cent formalin over night.
10. Wash in distilled water for 4 hours.
11. Dehydrate.
12. Imbed in paraffin, using oil of wintergreen.
13. Section at 10μ and mount.
14. Remove paraffin with xylol.
15. Remove xylol with absolute alcohol.
16. Cover sections with a very thin coating of celloidin to keep them on the slide.

17. Harden celloidin in 80 per cent alcohol.
18. Carry through 70 per cent, 60 per cent alcohol to water.
19. Tone in 0.5 per cent gold-chloride solution. This process, which brings out the black color and takes out the brown coloring, usually requires from 20 to 30 seconds and must be carefully followed with the aid of a compound microscope.
20. Wash in distilled water.
21. Retone in acidified gold-chloride solution (see below) for 20 to 30 seconds.
22. Wash well in about 4 changes of distilled water.
23. Fix in 10 per cent sodium thiosulphate for 2 minutes.
24. Wash in 2 changes of distilled water.
25. Dehydrate and clear in xylol.
26. Mount in Canada balsam.

Ammoniacal silver solution. Must be freshly prepared.

Sodium hydroxide, 25 per cent	2 ♏
Silver nitrate, 20 per cent	0.5 cc.

To this mixture add 20 cc. distilled water. Dissolve precipitate with ammonia, added drop by drop.

Acidified gold-chloride solution.

Gold-chloride, 1 per cent	3 ♏
Glacial acetic acid	3 ♏
Distilled water	10 cc.

As a check some nerves were stained according to Ranson's pyridine-silver method. Other nerves were studied for their myelin sheath with the aid of the Marchi stain. Again, in several instances the Schwann sheath-cells were colored with iron hematoxylin and Mallory's connective-tissue stain.

OBSERVATIONS AND COMMENT

After the cervical sympathetic chain had been cut and resutured the typical Claude Bernard-Horner syndrome occurred. The various stages in the disappearance of the signs of paralysis as observable in the size of the pupil, the position of the nictitating membrane, and the separation of the eyelids, are shown in Figure 89. The paralytic effect is noticed immediately after the nerve is sectioned, and as the animal comes out of the influence of the ether anesthesia the degree of the paralysis becomes more and more obvious. The nictitating membrane is slightly injected and obscures almost entirely the contracted pupil. There is marked enophthalmos and the eyelids are half closed. The condition remains virtually the same until the fifteenth day, when the nictitating membrane has become less prominent and the disparity in the size of the pupils has become less. On

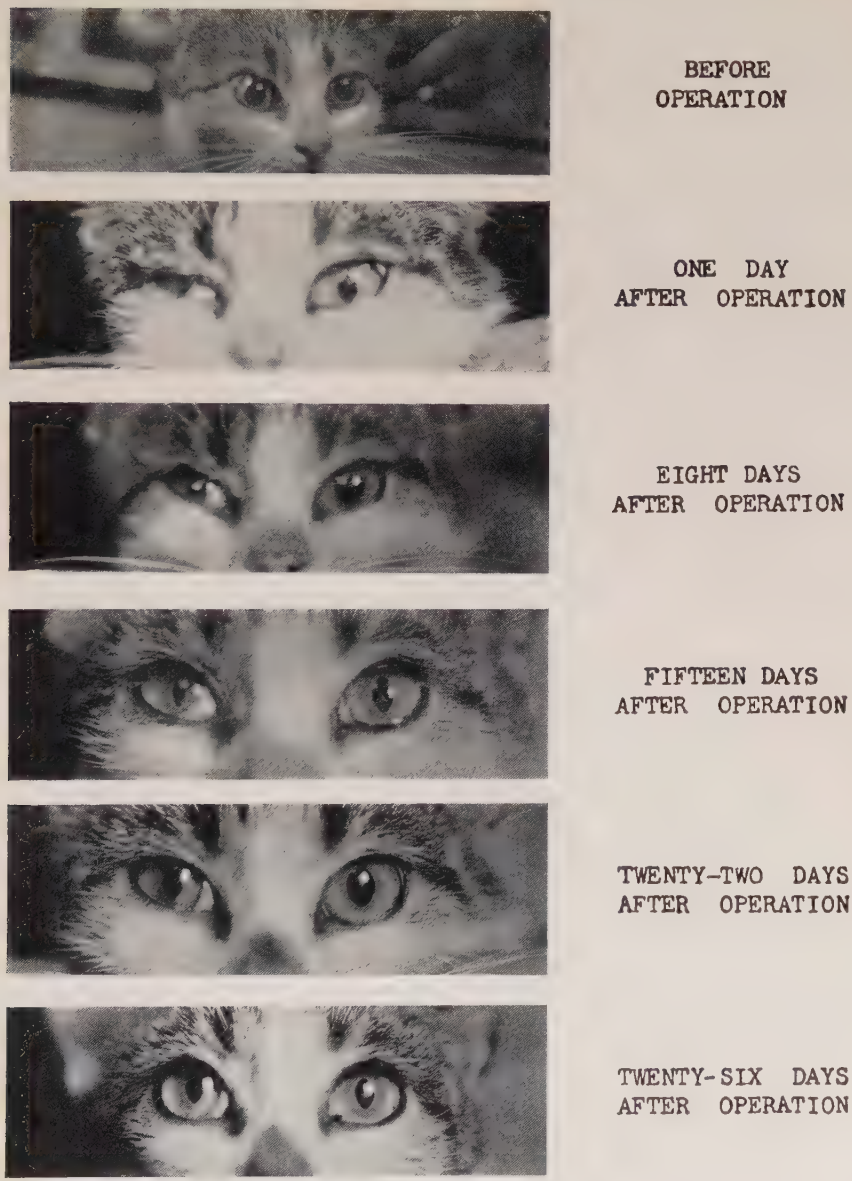

FIG. 89. Photograph showing the successive changes in the appearance of the eye following section and suture of the right sympathetic cervical trunk. The pupils were equal twenty-six days after the operation.

the twenty-second day the membrane is more retracted, and on the twenty-sixth day the pupils are equal.

Ordinarily, regeneration as determined by the equality of the pupils and the temperature of the ears, as well as by the retraction of the nictitating membrane, occurred by the thirty-fifth day. The longest case took sixty-eight days and the shortest, twenty-six days. The animals operated upon in the first part of the series required the longest time. The quickest recoveries were in those cats in which the sympathetic nerve was mobilized as little as possible.

Regeneration took place more rapidly in the younger adult animals; kittens were not used. Needless to say, the time of recovery depended a great deal on the care with which the anastomosis was made. It was not always necessary, however, to have apposition of the nerve-ends, because in two cases these ends were separated for a distance of a millimeter, and yet regeneration by the thirty-second and thirty-fifth days, respectively, occurred.

Langley (7) noticed incomplete regeneration of the lumbar sympathetic chain thirty-five and forty-eight days after section. He also observed almost complete regeneration of the cervical sympathetic chain at the end of three months (5). He described partial regeneration of this chain on the twenty-fourth day, and on the basis of these observations he postulated that regeneration might occur by the eighth to the twelfth day, since signs of ocular paralysis were disappearing at that time. The validity of this argument, however, may be questioned on the ground that the extreme degree of paralysis present during the first twenty-four hours after nerve-section was definitely less by the third day. Certainly no regeneration had taken place by the third day, even though an improvement was obvious. The difference in the appearance of the eye may well be due to a change in tone or posture effected through the parasympathetic nerve-fibers. Again, electrical stimulation of the proximal segment of a nerve which had been sectioned and sutured in a young adult cat twenty days previously, failed to show any evidence of regeneration. But it is possible that regeneration may take place in very young kittens as early as the eighteenth day. Langley used kittens and half-grown cats for his experiments, and never sutured the nerve, discounting the slight separation of the two ends after the nerve was sectioned.

This speed of regeneration compares quite favorably with the regeneration of the somatic nerves. However, the nerve-stretch which

underwent regeneration was short, being about 24 mm., measuring from the point of anastomosis to the middle of the superior cervical ganglion, which is about 7 mm. long. On this basis the rapid regeneration of twenty-six days would actually be slow, being less than a millimeter a day, whereas ordinary regeneration takes place at the rate of 1 to 2 mm. a day. It must be remembered, however, that some time is necessarily lost in the slight degeneration which takes place at the proximal stump preparatory to regeneration. Moreover, this period of twenty-six days indicated complete regeneration, whereas clinically the time of regeneration is usually terminated when the very first signs of regeneration appear. Granted even that the twenty-six-day period was relatively rapid, many other adult animals showed complete regeneration after intervals which were only slightly longer. In one animal the pupils were equal after thirty days; in two cats, after thirty-one days; in one, after thirty-two days; in one, after thirty-five days; and in five, after forty-four days.

Further evidence of an early rapid sympathetic regeneration was furnished by histological sections of the proximal nerve-end after a portion of the nerve had been previously resected. Here the new nerve-fibers had advanced into the blood-clot by the fifth day, whereas the sciatic nerve-fibers of the dog, according to the experiments of Kirk and Lewis (3), did not show the same degree of growth.

Sympathetic nerve-fibers also showed remarkable ability to bridge defects in their effort to bring about regeneration. Resection of 3.5 mm. was followed by partial regeneration after forty days and complete equality of the eyes after fifty-five days. Resection of 4 mm. required sixty-three days for complete recovery. In one animal in which the sympathetic chain was cut, the inferior end was sutured anteriorly to the sternomastoid muscle and the superior end to the deeper muscles of the neck, the nerve-ends being one inch apart. It was thus hoped to secure a permanent separation of the nerve-ends and to observe the subsequent eye-changes. But at the end of two hundred and seventy-five days the pupils were equal, and it was difficult to believe that regeneration had taken place when the nerve-ends had been tied and their ends separated for an inch, with muscle between. However, stimulation of the proximal nerve-segments with a weak current gave the typical response of retraction of the nictitating membrane and enlargement of the pupil. Furthermore, stimulation of the tissues between these two sutures showed that the regenerated

fibers had taken a course partly through the muscle and partly around it, following in the latter instance the opening originally made when the proximal end was drawn through the muscle. A study of the histological sections confirmed these avenues of regeneration. It is, of course, not uncommon for a nerve-trunk to bridge a gap of an inch; but when it is remembered that the nerve in question here was only about 0.6 mm. in diameter, and that its path was obstructed by muscle, this feat of regeneration becomes all the more remarkable.

In five animals the cervical sympathetic chain was cut and resutured distal to the first anastomosis. In all cases regeneration took place. Three cats required about the same time for regeneration of the second anastomosis as they did for the first. One animal required sixty-eight days for the second regeneration as compared with sixty-six days for the first, and one cat needed only thirty days for the second when it required thirty-five days for the regeneration of the first anastomosis. Langley (6) also had previously observed regeneration on section of regenerated nerve-fibers. Histologically the nerve in the author's experiments showed no changes of any greater importance than when a single section and suture were performed except that the segment between the two planes of section contained more fibrous tissue than the remainder of the nerve.

It was difficult to determine the early stages of regeneration. Some animals showed a marked retraction of the nictitating membrane, and only a slightly smaller pupil than on the control side. In several instances it was felt that regeneration might have taken place, but stimulation of the nerve failed to show regeneration. On the other hand, some animals showed even greater evidence of paralysis, but nevertheless stimulation showed regeneration. In these cases a strong stimulating current was always necessary. Thus, in one instance 5/32 of an inch of the right cervical sympathetic chain was resected, and fifty-six days later, although the right pupil measured only 3 mm. and the left 4 mm., and with the nictitating membrane protruding slightly, stimulation of the proximal nerve segment showed typical responses of regeneration.

It was furthermore noted that the pupil of the side on which the operation was performed, sometimes not only remained the same size as the control pupil, but became larger, Figure 90. This phenomenon was noted in four cats. In one animal the right pupil remained larger than the left for twenty-one days, and then became equal again. In

another case this disparity existed for thirty-seven days. In a third instance, 5/32 of an inch of the right cervical sympathetic chain was resected, and on the sixty-third day the right pupil measured 8 mm. and the left, or control side, only 6 mm. This case showed the greatest relative difference between the size of the pupils.

It may be well to mention in this connection that a cat in which the right cervical sympathetic chain was cut and sutured, developed an abscess of the left hind-leg at the time the regeneration of the sympa-

FIG. 90. Photograph showing effect of section and suture of the right cervical sympathetic chain. The subsequent regeneration of the nerve-fibers produced not only equality of the two eyes on the thirty-eighth day, but on the fifty-third day the right pupil was larger. The nictitating membrane, palpebral aperture, and position of the eye-ball were correspondingly affected.

thetic nerve was complete as judged by the equality of the pupils and the retraction of the nictitating membrane. The general condition of the cat became worse, it lost much weight, and refused food. In this moribund stage the right pupil was much larger than the left, and on the day before death the pupils measured 10 and 6 mm., respectively.

Not only were the pupils larger, but the nictitating membrane was more retracted than on the normal side, and the lid slits were wider. Langley (6) reported that in one cat in which the right cervical sympa-

thetic chain was cut, the pupil on the affected side was "at times" larger than the other from the thirty-first to the thirty-eighth day; the nictitating membrane on the affected side also was more retracted. This phenomenon may be explained on the basis that when the regenerating nerve is finally able to conduct nerve-impulses, their relatively sudden influx causes a greater response, since the iris and the nictitating membrane have assumed a posture which is much nearer normal than that of the early paralysis. Another explanation might be that the new nerve-fibers, dividing as they do on proceeding from the proximal stump, consolidate their entire conductivity in that particular division which makes connection with the superior cervical ganglion. This phenomenon was observed only in those cases in which a portion of the nerve was resected and the regenerating nerve was forced to bridge this defect. Sutured nerves apparently did not show this condition, or the effect was so transitory that it was not observed; nor was it observed in the three cases in which the sectioned nerve-ends were widely separated but which did show regeneration. It is possible that when the sectioned nerve-ends are slightly separated, more branching of the regenerating fibers occurs, and therefore more impulses reach the ganglion. But when the nerve-ends are carefully sutured, or when the ends are separated so widely that only a few fibers eventually establish a connection, this phenomenon is not noted.

As a rule, during the early part of the period of regeneration the pupil became larger and the nictitating membrane retracted more and more. During the latter part, however, the membrane retracted more rapidly, being similar in position to that of the normal side, while the pupil was still unequal. In one cat in which the nerve was resected and displaced to such an extent that regeneration was made impossible, the nictitating membrane had almost disappeared after a year, yet the pupil of the affected side was still smaller, measuring 5 mm., to 7 for the control side.

The nature of the illumination in which the examination of the eyes was conducted was also important. Often the affected eye seemed normal when viewed in subdued light, but when exposed to sunlight or to a pocket flash-light the same eye would still show a slight residual paralysis. Again, the consensual eye-reflex was also not normal; the affected eye, when it had reached the regenerated stage, showed some evidence of paralysis when a bright light was flashed into it.

The temperature changes in the ear were quite interesting. As soon as the cat was out of the influence of the ether anesthetic, the ear of the side on which the sympathetic chain had been cut was quite warm, particularly when compared with the normal ear. In one case, Figure 92, the difference in temperature was as high as 8.4°C. It must be added that in this case the room-temperature was low, and that the

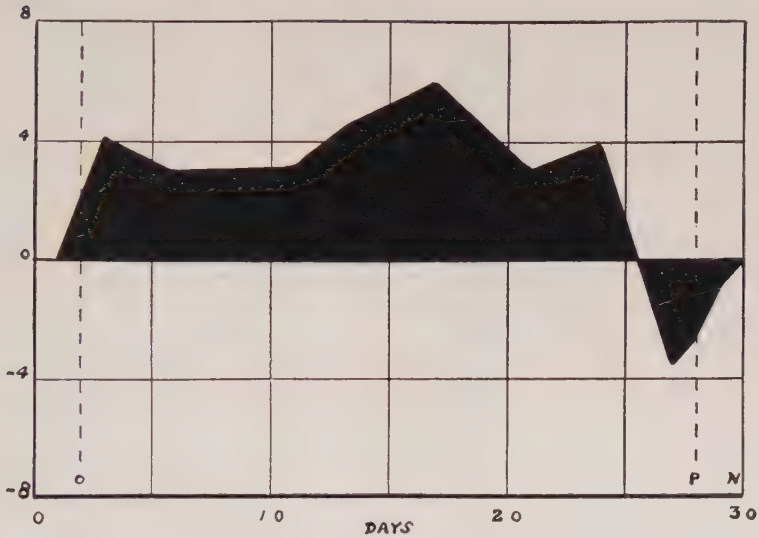

FIG. 91. Chart showing the temperature changes of the ears in the same animal as pictured in Fig. 89. The abscissae indicate days, the ordinates differences in degrees of temperature (centigrade) between the two ears. All values above the base-line represent the degrees by which the right ear was warmer than the left, and those values below this base-line, the extent to which the left ear was warmer than the right. It will be noted that immediately after section and suture of the right cervical sympathetic chain, at *O*, the right ear was warmer than the left, and that this condition continued until the twenty-fourth day, when there was a sudden reversal of temperature, the left ear being warmer two days before the pupils were equal, as indicated by *P*. On the twenty-eighth day the temperature of the ears was again equal.

colder the room, the greater was the temperature difference between the two ears. In two animals in which the nerve was sutured the temperature of the two ears, as well as the rectal temperature, was taken (Figs. 91 and 92). In Figure 91 only the respective differences for these temperatures are given, and it will be seen that on the affected

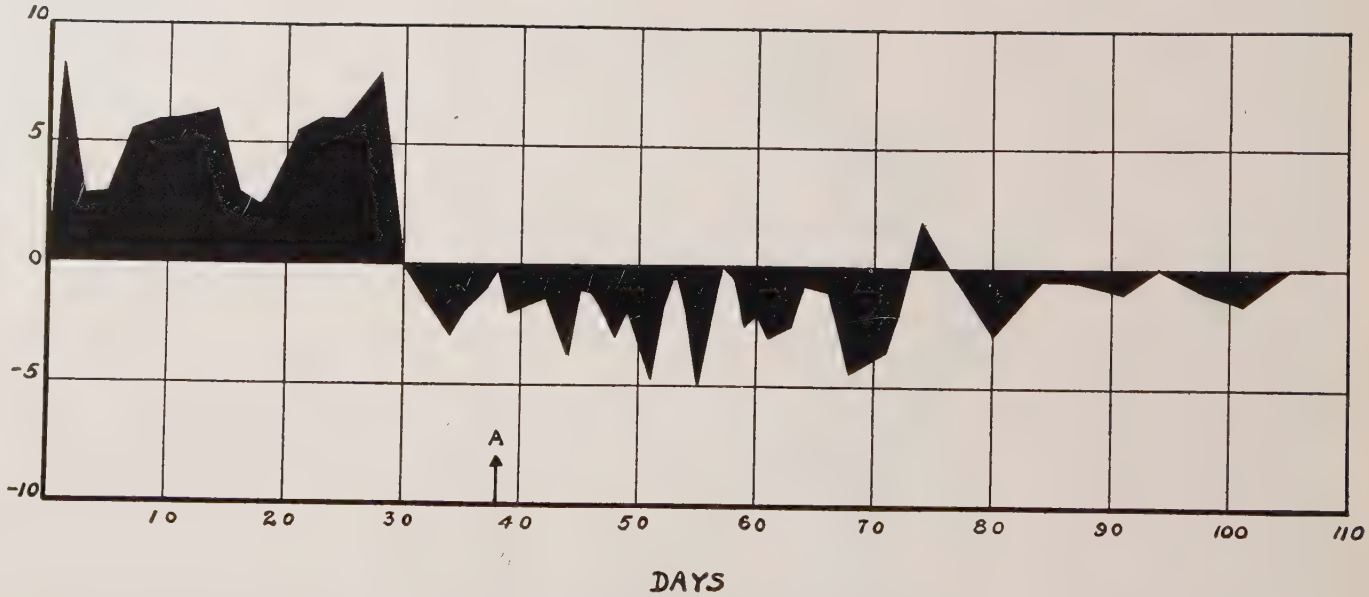

Fig. 92. Chart showing the temperature changes in the two ears for a longer time than is given in Fig. 91. After section and suture of the right cervical sympathetic chain the right ear was warmer until the thirtieth day, when the temperatures were equal. The left ear was then warmer until the thirty-eighth day, marked by *A*, when equality was again present. On this day also the pupils were equal. From then on, the left ear remained warmer to a varying degree until no difference was noticed from the one hundred and fifth day.

side the temperature was always greater until a few days before regeneration was complete as judged by the equality of the pupils and the retraction of the nictitating membrane. At this time a sudden reversal of temperature occurred, making the side on which the operation was performed colder than the normal one. This state of affairs, however, did not continue long, for when regeneration had been established the temperatures were again equal. In Figure 92 the same phenomenon was again observed. Furthermore, in this animal the temperatures were again recorded not only directly with thermometers, but also with the aid of a thermocouple. It was found, however, that the temperature of the control ear varied so widely that the difference exceeded the sensitivity of the galvanometer. In fact, the temperature of the normal side frequently varied a degree centigrade at successive half-hour intervals.

It is interesting to note, as can be gathered from Figure 92, that after the first period of thirty days following the nerve-suture in which the right ear was warmer, there occurred another period of about the same length, in which the left ear was warmer. However, the left ear was never as relatively warm as the right ear had been previously. The temperature difference subsequently became still less, with higher values on the normal side. Finally, on the one hundred and fifth day after operation, equality was reached and continued.

It is quite obvious that the increase in temperature of the right ear after section of the corresponding nerve can be explained by the absence of vasoconstrictor impulses, as was pointed out by Claude Bernard in 1852 (1). On the same basis it may be argued that once the newly regenerated fibers are able to mediate vasoconstrictor impulses, the peripheral blood-vessels are suddenly flooded with such a mass of constrictor impulses that the previously warm ear at once becomes correspondingly cold. This transition, which is well shown in Figures 91 and 92, is rapid and striking. In Figure 91 the temperatures were equal again on the twenty-eighth day, whereas in the animal whose curve is given in Figure 92, equality in temperature was not approached again until the thirty-eighth day, the day on which the pupils were also equal. Why the equality in temperature occurred so much later in this animal than in the first one, it is difficult to explain. It may be ventured that some animals may require a longer time to readjust their vasomotor control, particularly if they are old. In fact, the animal represented in Figure 91 was a young adult cat,

whereas the one shown in Figure 92 was more mature but not old. This process of readjustment may also depend upon an increased number of fibers which possibly grow out from the proximal stump, connect with the ganglion-cells of the superior cervical ganglion, and send an increased stimulus to the peripheral vessels; younger animals probably have a greater proliferation of nerve-fibers.

Apparently regeneration is to a certain extent selective, the vasomotor fibers functioning first. Certainly a reversal of the ear-temperature occurred two days before the pupils were equal. Whether this selectivity has any deeper biological significance as far as self-preservation is concerned cannot be stated. However, it may be possible that the vasomotor control with its attendant heat-regulating influence is more essential for the self-preservation of the animal than is its acuity of vision.

Again, it may be argued that the relatively early return of the vasomotor effect might have been due to other factors, possibly to collateral innervation. But this view should not be considered seriously because one cat in which the right cervical sympathetic chain was resected in such a manner that regeneration did not occur, still showed typical signs of vasomotor paralysis a year later. The temperature of the right ear was 34.5°C. and the left, or control side, 32.3°. The right pupil measured 4 mm. and the left, 8 mm.

It was noticed, furthermore, that when the cat was put under an ether anesthetic after the pupils had become equal, the nictitating membrane would protrude more and the pupil would be smaller than the corresponding structures on the normal side. As soon as the anesthesia had worn off, these signs of partial paralysis disappeared again. The extent of this paralysis was greater the nearer this test was made to the time when regeneration had restored the size of the pupils to equality. In one animal this phenomenon was still slightly present a year after regeneration had taken place. Langley (6) had noticed that the nictitating membrane would sometimes cover one-third of the eye after the animal was put under the influence of chloroform following a previous nerve anastomosis with other nerves, such as the vagus. Apparently the difference in the size of the pupils was not noticed, and it is difficult to believe that it did not exist, because it is unreasonable to expect only the fibers going to the nictitating membrane to be affected.

Electrical stimulation of the peripheral segment showed that it still

conducted impulses very well for four days after the lesion. In one case conduction was still possible after seven days. It is reasonable to suppose, then, that the sympathetic nerve-fibers are more viable than the somatic fibers. Whether this property is due to the relative scarcity of myelin can only be conjectured, but the less myelin a nerve-fiber has, the less differentiated it is, the greater are its inherent properties of viability and regeneration. Although many of the nerve-fibers of the cervical sympathetic chain are myelinated, there are also a great many that are non-myelinated; and when one compares the myelinization of the neighboring vagus nerve, then it must be plain that the amount of myelin in the cervical sympathetic chain is relatively small.

In three cats in which the cervical sympathetic nerve-trunk was examined from forty-one to forty-nine days after suture, it was found necessary to apply a stronger electrical stimulus to the distal segment to produce the same peripheral response as was elicited by a weaker current applied to the proximal segment. This difference in current was not great but always amounted to a rotation of 20 degrees of the secondary coil.

In addition, in these three animals it was observed that the peripheral segment showed a loss of irritability virtually amounting to fatigue. Repeated electrical stimulation with a minimal current soon failed to produce a peripheral reaction; however, the same type of stimulation to the proximal segment elicited a response for a much longer time. Thus the regenerated nerve had a loss of irritability, but showed normal conductivity.

Gross examination of the distal segment during the period of regeneration showed that it soon lost its blue-gray color as well as its compact appearance, and became instead larger, with light purplish discoloration and gelatinous appearance. After regeneration had set in, the peripheral nerve-trunk became progressively more like the proximal segment, and in one case in which the nerve was examined four hundred and thirteen days after suture, the proximal and distal segments appeared alike.

Figure 93 shows the appearance of the cervical sympathetic chain one hundred and eighty-four days after 5/16 of an inch had been resected. Numerous white bundles of about the same size, coursing in an almost straight line, are seen to connect the two bulbous ends of the sectioned nerve. Stimulation of these fiber-bundles caused the typical ocular responses of the normal nerve.

Histological examination of the material obtained from the animals described above is incomplete, and testifies, furthermore, to the proverbial fickleness of nerve-stains. However, the study of serial sections of the cervical sympathetic nerve two days after a portion of it was resected, showed that the proximal stump had numerous club-shaped endings of various sizes. Many fibers were fragmented at their ends. The distal stump showed the same characteristics except that the fragmentation was present much further along the fiber, and the

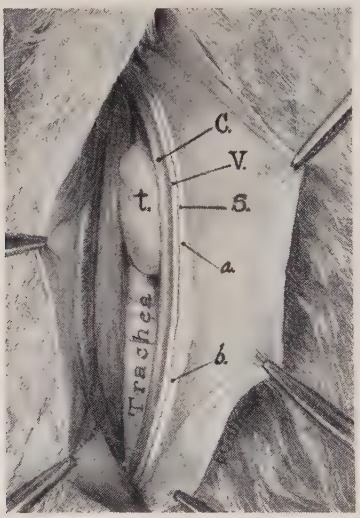

FIG. 93. Drawing showing how the regenerating nerve-fibers bridged a gap of 5/16 of an inch in the right cervical sympathetic chain. The nerve-ends, *a*, *b*, of the sympathetic nerve, *S*, are slightly thickened, and are joined by numerous bands. *T*, thyroid gland; *C*, common carotid artery; *V*, vagus nerve.

end-bulbs were fewer and smaller. Some of the nerve-fibers were unusually thick and larger than in the proximal segment.

On the fourth day new fibers had grown beyond the line of section into the blood-clot. The outgrowth was characterized by the splitting of the fibers into two or more processes which frequently had pointed extremities and did not show the elaborate spirals, skeins, buttons, and end-bulbs described by Perroncito (10) for the somatic nerves. A branching of these nerve-fibers was frequent, and it was common to find many connections, as in a plexus, between different fibers.

By the tenth day the nerve-fibers had grown well into the organizing blood-clot. It was noticed that these fibers seemed to proceed forward mainly in the form of bundles or sheaves, each bundle having five or more closely packed nerve-fibers with a surrounding sheath which it was difficult to study since it was not stained differentially. The adjoining connective tissue did not cause the nerve-fibers to reverse their direction, or to coil up into bundles and skeins, or to assume the twisted, interlaced, and massed appearance so characteristic of an amputation

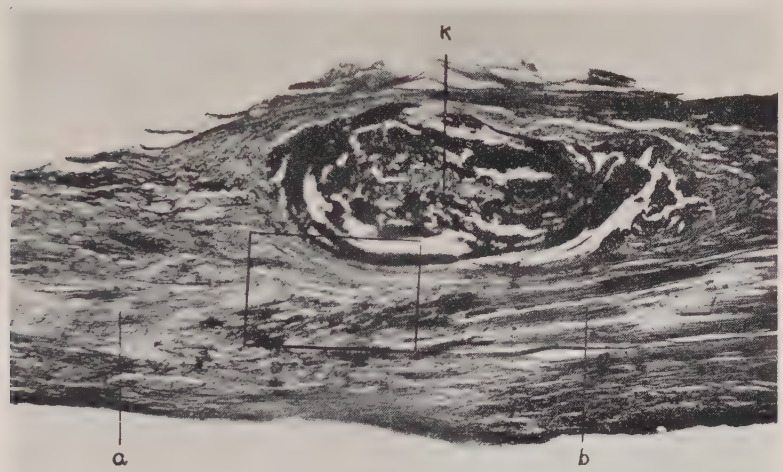

FIG. 94. Drawing showing a longitudinal section of the cervical sympathetic chain, *S*, which was sectioned and sutured at a point marked by the silk knot, *K*, thirty days previously. The vagus nerve is indicated by *V*. The proximal segment is marked *a*, and the peripheral, *b*. The outlined area is reproduced at a higher magnification in Fig. 95. (Modified Cuajunco stain. × 80.)

neuroma. It seemed, in fact, as if the regenerating sympathetic fibers, in contrast to the somatic fibers, were able to progress favorably in, and be hampered little by, connective tissue. But when it is remembered that the sympathetic fibers are widely distributed normally in loose connective tissues, then this relationship may not seem so unreasonable, even though the fibers here described are preganglionic and in many respects closely allied with the somatic fibers.

After the regenerative processes had united the proximal and distal nerve-segments, the region of the anastomosis was characterized by a moderate irregularity in the position of the fibers. In Figure 94 the anastomotic area is relatively short, and can be seen to joint the compactly arranged fibers of the two segments, *a* and *b*. A higher magnification of the area marked out on Figure 94 is shown in Figure

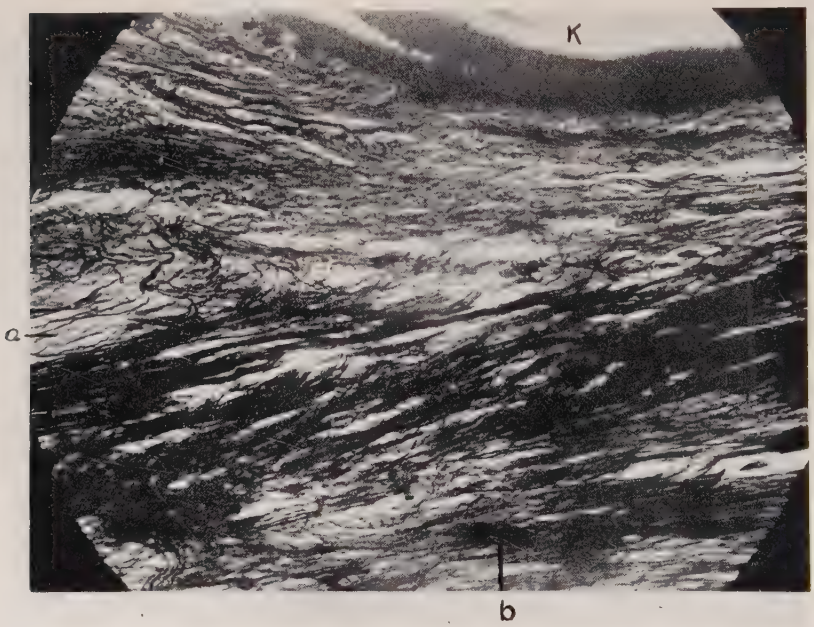

Fig. 95. Drawing showing longitudinal section of cervical sympathetic chain. A higher magnification of the area indicated in Fig. 94. Note the short gap, indicating the anastomosis between the proximal, *a*, and the distal, segment, *b*, of the cervical sympathetic chain; a portion of the silk knot in the epineurium is at *K*. (× 350.)

95. Here individual nerve-fibers can be traced almost across the anastomosis. A large overproduction of fibers is not apparent, probably because the anastomosis was performed sufficiently well so that a large space did not separate the two ends. The silk thread, *K*, indicates the point of union.

SUMMARY

After the cervical sympathetic chain in cats was cut and sutured, it was found that complete regeneration occurred on an average by the thirty-fifth day; the most rapid recovery was by the twenty-sixth day. The regenerating fibers were able also to bridge defects in continuity extending for an inch and having the respective nerve-ends separated by muscle-tissue. Some regeneration was found to be present even though the size of the pupil, the protrusion of the nictitating membrane, enophthalmos, approximation of the eyelids, and elevated temperature of the ear still gave evidence of a partial paralysis. Section and suture of the regenerated portion of the nerve was again followed by regeneration, which took place about as rapidly as after the first section. Generally the nictitating membrane retracted before the pupils were equal. The temperature of the two ears, however, became equal before any of the other signs of paralysis had completely disappeared, thus indicating that regeneration was possibly selective, with vasomotor paralysis disappearing first. The ear which during the paralytic stage had been warmer, after regeneration became colder for a time. In several instances the pupil on the regenerating side became larger than the one on the control side; particularly was this true when a portion of the nerve had been resected. The recently regenerated nerve frequently showed lessened irritability but had normal conductivity. The peripheral segment was able to conduct electrical impulses for as long as seven days after nerve-section. When a cat in which the cervical sympathetic chain had regenerated, following section and suture, was put under the influence of ether, a moderate degree of sympathetic nerve-paralysis would again appear but this would remain only as long as the anesthetic was continued. Neuroma formation was present to a slight extent; but the outgrowing fibers were not turned back, twisted, or coiled up to the same degree as in the ordinary somatic nerve. The newly formed fibers found their way through the connective tissue, not so much as individual axones, but in bundles. The rapid growth of fibers at the proximal nerve-end was characterized, furthermore, by an increase in the number of fibers by division, as well as by the absence of the Perroncito spirals.

DISCUSSION

The following questions submitted to Dr. Lee before the Commission, together with the answers to them, are here reported verbatim.

Dr. Cobb: The clinical observations of the animals operated upon, appear to have been a somewhat unreliable guide as to the presence of regeneration. The best index was evidently the stimulation of the sympathetic nerve electrically. Could you tell us how often and in how many cases this was carried out, both to the distal and the proximal segment of the cut nerve?

Dr. Lee: This work was carried out on thirty-seven cats, and in all cases the regeneration was checked by electrical stimulation, both proximally and distally. Not only that, but it was checked also by histological sections, even though electrical stimulation was the only method which was to tell definitely whether there was regeneration or not. Frankly, I fail to see why electrical stimulation proximal to the point of union should not be considered satisfactory evidence of regeneration.

Dr. Pollock: I should like to ask how far distally the histological studies were carried on in the experiment of the cat which had such a remarkably early regeneration.

Dr. Lee: We have sections at the line of anastomosis, one of which I showed as the longitudinal section; we also have cross-sections very close to it, both proximally and distally, but none extending completely to the superior cervical ganglion.

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CHAPTER XIX

THE NERVE-SUPPLY OF THE CEREBRAL BLOOD-VESSELS

An Histologic Study[1]

GEORGE B. HASSIN, M.D.

FRANÇOIS-FRANCK (6) justly stated that the vascular innervation of the central nervous system may conveniently be studied on the blood-vessels of the pia, for the latter "practically belong to the brain substance itself." It must also be conceded that the vasomotor nerves of the pia are derived from the cervical sympathetic nerve-supply of the internal carotid and the vertebral arteries. The vertebral system innervates the blood-vessels of the pons, medulla and cerebellum. The carotid system supplies the rest of the cerebral vessels. The pia receives additional—parasympathetic—nerves from the third, seventh, ninth, tenth and also some nerve-fibers from the sixth, eleventh and twelfth cranial nerves. Some nerves have apparently nothing to do with the vascular innervation, for they end freely in the connective tissue. Some such fibers are probably sensory.

METHODS OF STUDY

Ordinary dissecting methods of studying the vascular nerves may be applied only to the larger blood-vessels, such as those of the carotid and the middle cerebral arteries. For smaller blood-vessels, the refined, so-called "macro-microscopic" methods of Worobiew (41) and his pupils (11) are valuable; while the nerves of minute blood-vessels (arterioles, venules, capillaries) can be studied only with special microscopic staining methods. Of these the most important are Ehrlich's intravitam methylen-blue method and its modifications, and the silver-staining method of Schultze. The methylen-blue method was used by the author in the form of intracerebral injections of a few drops of 1 per cent solution of methylen-blue. The pia arachnoid, as well as the contents of the subarachnoid space, stained readily, but the nerve-fibers remained unstained. This method has

[1] From the Pathologic Laboratories of the University of Illinois and the Illinois State Psychopathic Institute, Chicago.

been used by the author on a limited number of rabbits and was discarded in favor of the silver-staining method of Schultze. It has been employed as follows:

Specimens consisting of small pieces of the pia were hardened in a 10 per cent solution of formalin; 2 days later they were carefully dissected and were placed *in*

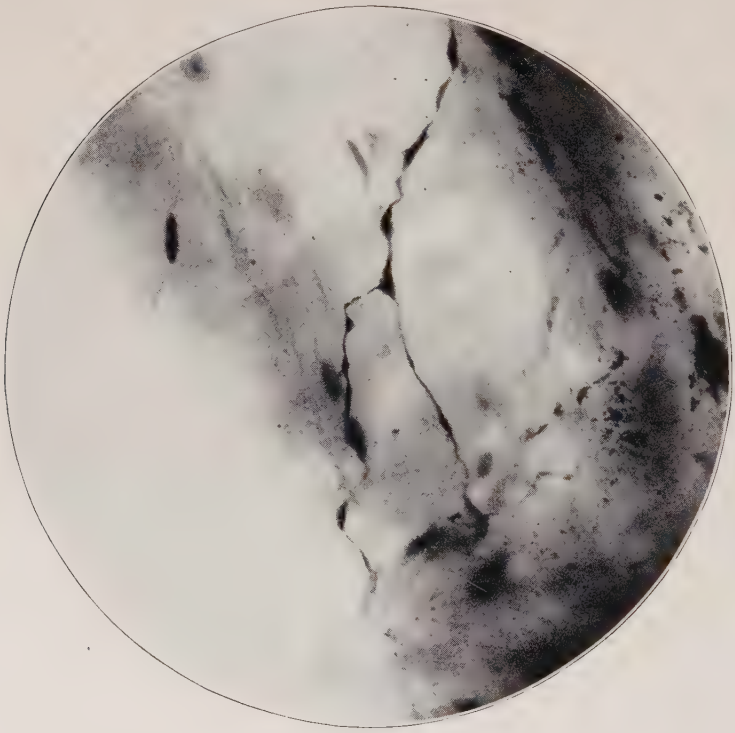

FIG. 96. Dog's brain. The adventitia of a small artery (0.12 mm.) shows non-medullated varicose nerve-fibers. The varicosities are especially marked near or at the point of bifurcation. The left fiber also shows two Schwann cells, one of which (the lower) is adjacent to the varicosity. Other nerves can be seen to the right; those to the left are indistinct (out of focus). (Schultze-Stöhr silver stain. × 640.)

toto, for 24 hours, in a 20 per cent dilution of normal (4 per cent) stock solution of sodium hydroxide. The specimens were then washed in several changes of distilled water for about 1 hour, and were afterwards placed in a 10 per cent solution of silver-nitrate for from 12 to 16 hours. They were then reduced in a mixture of hydroquinone-formalin. This mixture (hydroquinone, 2.5 gm., distilled water,

100 cc., formalin, 5 cc.) is also kept as a stock solution and before being used, should be diluted, 1:80 or 1:20. The author has been using a 1:80 solution, that is, 1 drop of hydroquinone-formalin to 79 drops of distilled water. If the solution becomes somewhat cloudy, it should be changed. Here the tissues stay for about 1 hour and are then examined under the microscope for the presence of nerve-fibers. As soon as such fibers are noticed, the tissues are rinsed in distilled water (twice), passed through alcohol (95 per cent) carbol-xylol and mounted in Canada balsam.

After treatment, the fibers appear as black threads; the myelin is brownish, and the rest of the tissues are pale yellow or brown, according to the length of time they have been kept in the hydroquinone-formalin solution. If kept too long, all the tissues turn dark; if too short a time, they show too pale. For this reason the tissues should be examined before they are passed from the reducing solution to water. Fresh material gives the best pictures, but the author has also obtained good results from quite old specimens.

With this rather simple method Stöhr, Jr. (30-36) followed the nerve-supply of the blood-vessels of the pia, chorioid plexus of the third and fourth ventricles and of some of the visceral organs. The pictures so stained are striking. Figure 96, for instance, represents the nerves of a minute artery (0.12 mm.) of the peduncular pia from a dog's brain. The nerve appears here as a curved, varicose, zigzag thread, accompanied by the nuclei of Schwann. The latter usually run parallel to the nerve-fibers; often they are closely adjacent to them, flattened and thinned. They are of a large size, rich in chromatin, and widely separated from one another. In some instances, the nerve-fibers are bordered by, or enclosed within, broad granular brownish bands (Fig. 97). These often appeared as thick granular fibers, freely scattered; or they could be traced to large cell-bodies (Fig. 98) which were also granular, possessing a large, pale nucleus, a nucleolus and numerous branching processes. The cells showed as multipolar stellate bodies; some were spindle-shaped and their nuclei were oblong and flattened. Whatever the form and the size, their processes did not form anastomoses. The cell-bodies were much larger than ganglion-cells, which they resemble, but they possessed no fibrils and generally appeared as massive, rather coarse structures. These cell-bodies are the so-called chromatophores, pigment-producing connective-tissue cells. They were especially numerous in the basal pia of the brain where, as noted, there is also an abundance of sympathetic nerve-fibers. As Figure 97 shows, these cells are present also in the walls of the blood-vessels themselves. Among these cells and their processes are seen the nerve-fibers winding along, running

parallel to the long axis of the blood-vessels and sometimes blending with or enveloped by them (Fig. 97). The fibers can be recognized by their dark color, by their varicosities and, in many instances, by the accompanying nuclei of cells of Schwann. Quite often did the nerve-fibers travel together. In Figure 99, a set of eight fibers is seen run-

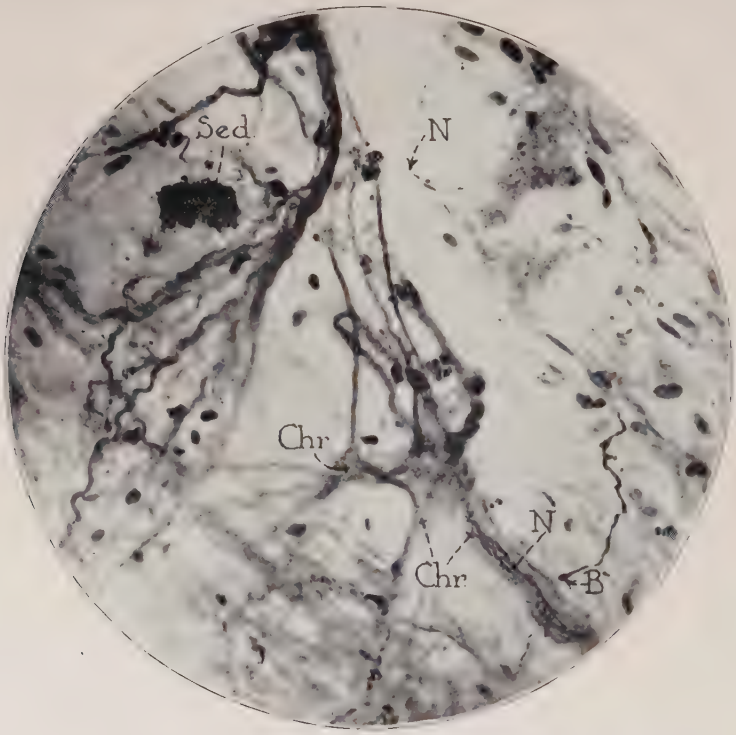

FIG. 97. Dog's brain. The centre of the picture is occupied by chromatophore (*Chr.*) cells and their large processes, of which the right lower one contains several dark thin nerve-fibers (*N*). To the right of this chromatophore process is a small winding nerve-fiber ending, near the process, in a small bulb (*B*); *Sed.*, sediments. Size of the blood-vessel, 0.4 mm. (Schultze-Stöhr method. × 320.)

ning parallel, all devoid of myelin and some of them exhibiting marked varicosities. Such are especially well seen in single nerve-fibers (Fig. 96) and their branches. Other nerve-fibers formed a network (Fig. 100) or plexuses of non-medullated fibers. These were mainly periadventitial, as they could easily be discerned over the adventitia. Though also present (Fig. 101) in the muscle-tunic, they were here

much more difficult to observe. Some nerve-fibers here were minute, thin and granular twigs running as dotted lines (Fig. 102) parallel to the nuclei of the muscle cells which they sometimes enveloped. In still rarer instances, the vessel-walls contained formations much resembling ganglion-cells (Fig. 103). Their cell-body and the narrow portion corresponding to the site of the nucleus were rather densely

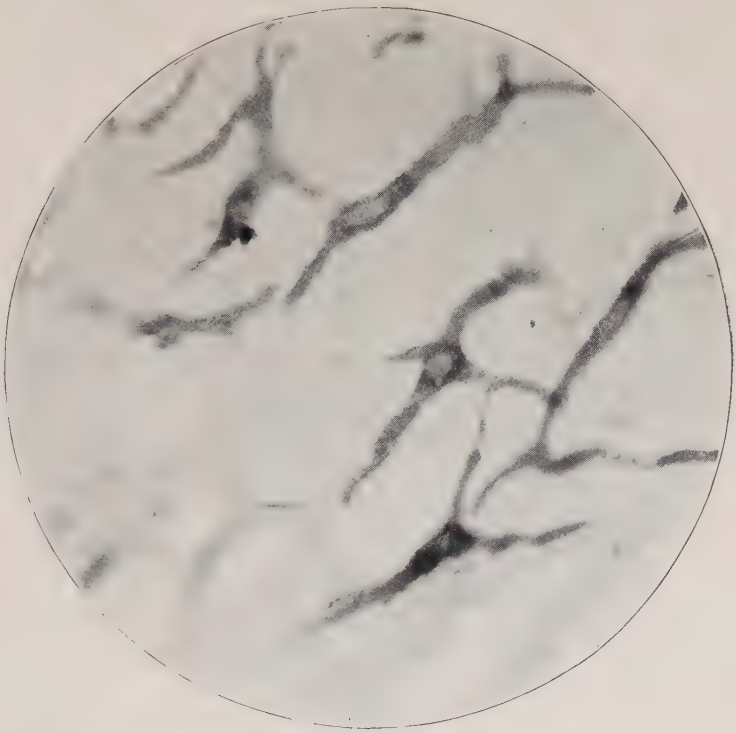

FIG. 98. Dog's brain. Chromatophore cells, explanation in text. (Schultze-Stöhr method, counterstained with Alzheimer-Mann stain. × 680.)

stained, their processes were paler, but, like the cell-body, they appeared homogeneous and structureless.

It was not possible to establish the connection of the fibers with the vessel-wall, that is to say, the mode of their termination. As a matter of fact, it was not always easy to follow the end-stations of the vascular nerve-fibers. As a rule, these could be traced over a long stretch,

down to the smallest branches. Here (Fig. 104) they were represented by a thin, black, curved thread extending over the wall, which terminated sometimes in bulb-like, knob-like or nodular enlargements (Figs. 104 and 105). In other rarer instances the terminations resembled "convolutes" of non-medullated nerve-fibers with end-platelets, as pictured in Figure 103. Like the thin, granular fibrils

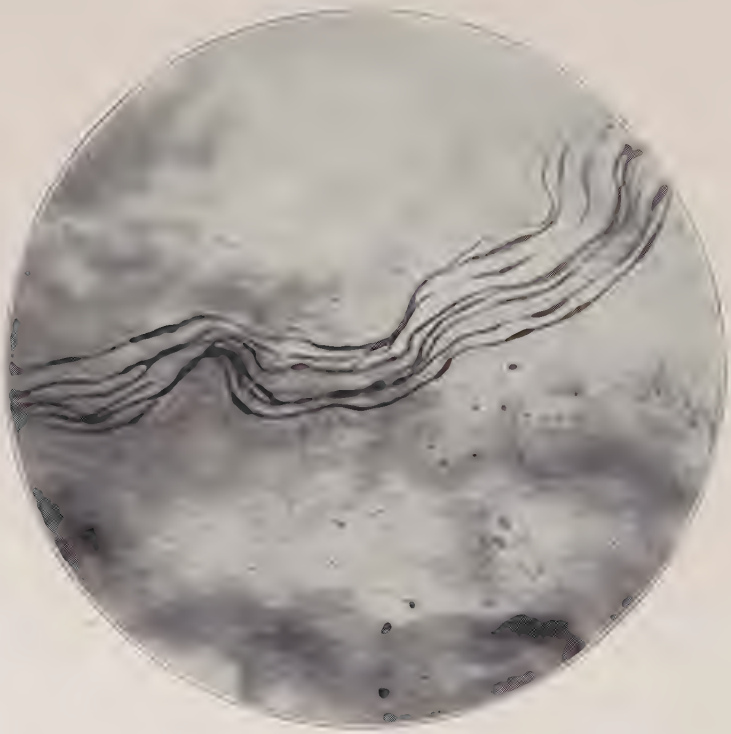

Fig. 99. Dog's brain. The adventitia of a small blood-vessel (size, 0.34 mm.) is crossed by a bundle of eight nerve-fibers, some of which exhibit marked varicosities. (Schultze-Stöhr silver stain. × 640.)

seen in Figure 102, the foregoing formations were probably the endings of vascular nerve-fibers.

The observations described were all made on the pia of the base of the brain—the pons, cerebellum, medulla and peduncles of the brains of man, dogs, guinea-pigs and rabbits. The pia of the cortex of the brain also showed the presence of the vascular nerves, but over

the convexity of the brain the pial blood-vessels were practically devoid of them. In the gray and white substances, they were absent entirely. None could be found even in the pial prolongations, between the convolutions.

SUMMARY OF HISTOLOGIC FINDINGS

The pial blood-vessels, except the capillaries, possess a wealth of nerve-fibers within the adventitial and muscular layers; some fibers

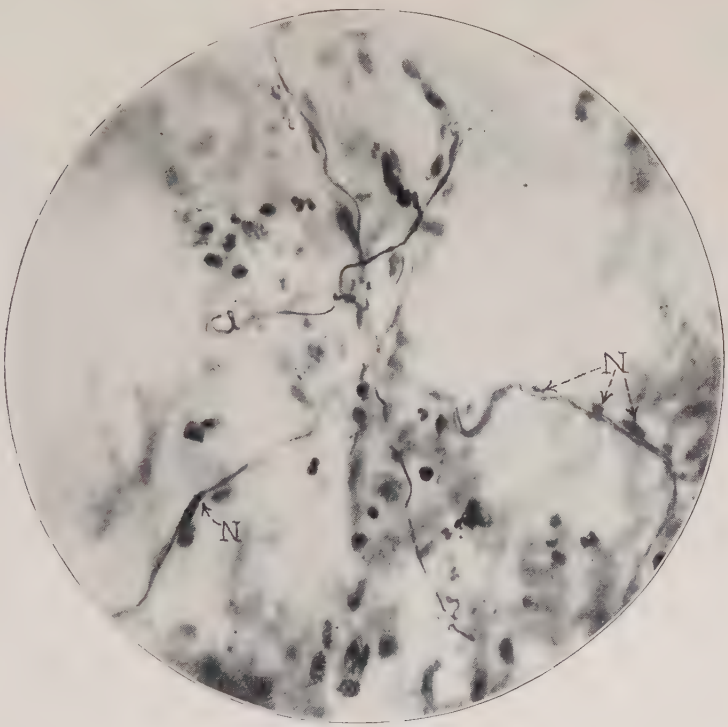

Fig. 100. Dog's brain. Network of vascular nerve-fibers (size of the blood-vessel, 0.6 mm.). The fiber to the right (*N*) is covered with myelin and shows several Schwann cells. (Schultze-Stöhr method. × 420.)

are medullated; the majority are naked, represented by varicose threads; they run singly or in bundles; occasionally, they give off branches and form networks; the fibers show free endings in the adventitia, in the form of bulbs; in the muscle-layer the endings are

Fig. 101. Dog's brain (peduncular pia). Network of nerve-fibers on the muscularis. Size of the blood-vessel, 0.6 mm. (Schultze-Stöhr method. × 280.)

less definite; the vascular nerves are generally abundant at the base of the brain, where they are often mixed with so-called chromatophore cells. No nerve-fibers were found in the blood-vessels of the brain substance itself.

COMMENT

The findings here recorded are essentially analogous to those of Stöhr, Jr. In a number of brilliant contributions (30–36) he showed that the blood-vessels of the pia and the chorioid plexus possess a wealth of nerve-fibers. Although partly confirmed by Berger (2), Stöhr's investigations may be considered the only real proof of the presence of nerve-fibers in the pial blood-vessels. It is quite true that a number of older investigators—Retzius (23), Obersteiner (20), Morison (18), Huber (9), Gulland (8), Hunter (10), and others—described formations which they considered nerve-fibers. Of these, only Retzius and, to some extent, Huber appear to have furnished convincing descriptions. In the arteries of the chorioid plexus of a white rabbit, Retzius found muscle-cells that contained finest threads, in the form of varicose terminations. The periarterial nerve-plexuses not only formed nets, but also emitted, here and there, varicose branches which lay adjacent to the muscle-layer of the arterial wall, terminating free. Yet even Retzius' observations differ from those recorded by the author; Stöhr states that the findings of other investigators, including even these of Huber, resembled little those described by himself.

A few words should be added with reference to the chromatophore cells. As stated previously, they much resembled ganglion-cells. The latter are occasionally seen in the chorioid tela, the pia and, according to Stöhr, in the deeper adventitia, between the latter and the media. They are much less common than the chromatophores which in the author's specimens were conspicuous by their huge size, the enormous length of their processes, their granular appearance and the absence of a fibrillary structure. Their significance is not clear. Nor is it possible to account for their prevalence in areas rich in sympathetic nerve-fibers, or for the occasional presence of the latter within their processes. Whatever their nature, they certainly have nothing to do with the innervation of the intracranial blood-vessels. These possess a definite neuromuscular apparatus the activity of which is responsible for the changes in the lumen of the blood-vessels—their contraction and dilatation. It was assumed that a similar mechanism is present also in the capillaries and precapillaries, regardless of the fact that these possess neither muscle-cells nor nerve-fibers. It is true that the latter may be seen on the capillary wall, but without giving off branches or exhibiting endings. One may also assume

that the minute blood-vessels and the capillaries are utilized by the nerve-fibers as conducting pathways or that they accidentally intermingle. Some investigators, however, hold that the association of, or the connection between, the capillaries and the sympathetic nerve-fibers is not an accident but is a definite neuromuscular structure.

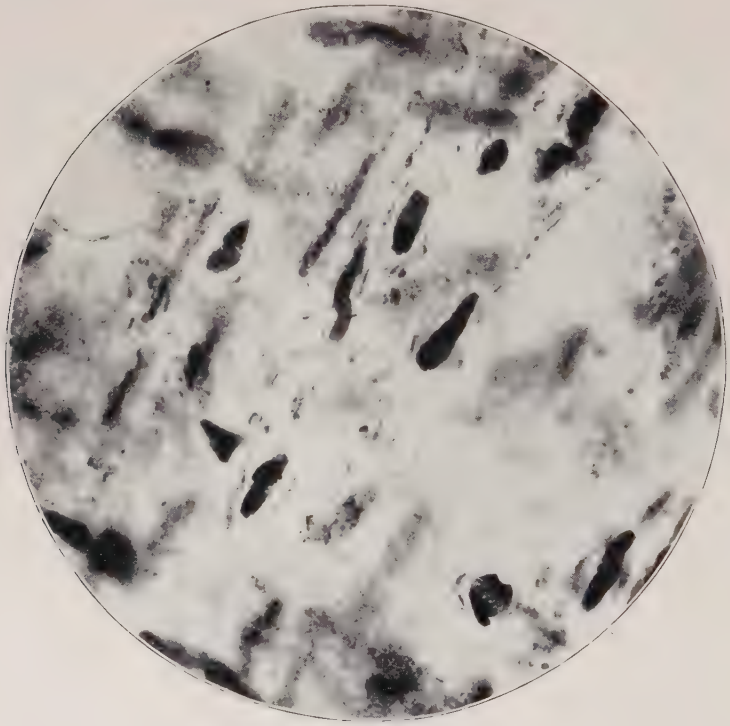

Fig. 102. Human brain. Muscle-tunic of a small blood-vessel. The black bodies are nuclei of the muscle-fibers, in many instances surrounded by delicate granular nerve-fibers. These are evidently the terminal branches. Size of the blood-vessel, 0.14 mm. (Schultze-Stöhr method. × 780.)

Its neural component is the sympathetic nerve; the muscular component is represented by the so-called Rouget cells or pericytes (Zimmerman (42), Ebbecke (5)). The latter stimulated by the sympathetic nerve-fibers cause contraction of the capillaries (Krogh (12, 13)). The changes observed by Golubew (7), Ljetnik (15), Tarchanoff (37), Rouget (25, 26), Steinach and Kahn (29) in the walls and lumina of the capil-

laries in the larvae of Amphibia or in older animals, have been ascribed by Krogh also to the presence and activity of the foregoing cells. Vimtrup (38) describes them as situated outside the capillary wall, over the "endothelial" membrane; they are more massive than the

FIG. 103. Adult human brain. The large round mass (*G*) in the lower portion of the picture is evidently a ganglion-cell with dendrites; the broad, pale band to the left is a chromatophore (*Chr.*) process; at *Conv.* is a "convolute" of nerve-fibers enclosing pale, round cells forming an end-platelet; the solid dark lines are nerve-fibers. The majority of the nuclei are Schwann cells. Size of the blood-vessel, 0.33 mm. (Schultze-Stöhr method. × 540.)

endothelial cells; they are either round or oblong; their axis is parallel to the long axis of the blood-vessel; the nuclei are enveloped by a cytoplasm which thins out into sharp processes. These run parallel to the capillary, but they surround it with their processes, which may be numerous and cause not only its contraction but even its

complete obliteration. Krogh and his pupils concluded that these contractile cells of the capillary wall cause an independent activity of the capillaries; that the entire vascular system of the brain is thus provided with a nerve-apparatus which controls the cerebral circulation, and that the capillaries possess a tonus of their own, exhibiting phenomena of contraction and relaxation.

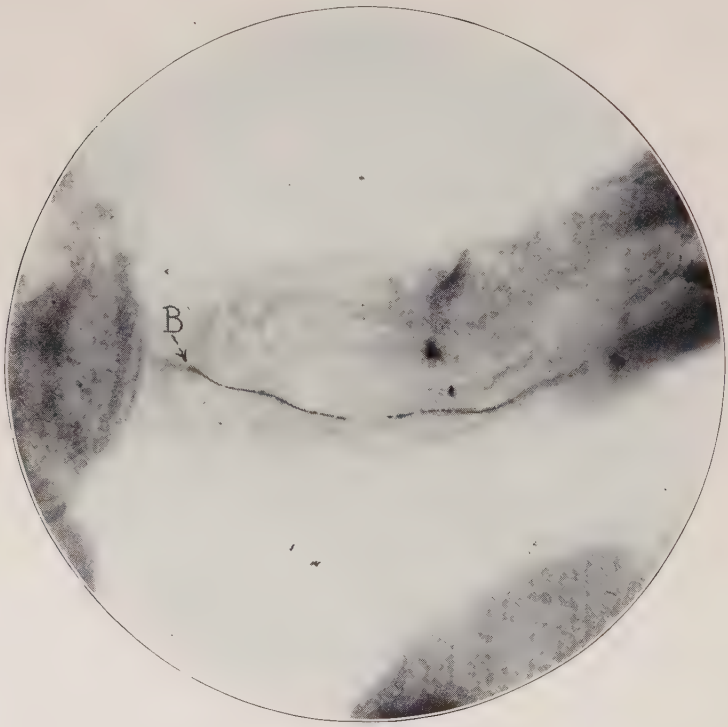

Fig. 104. Adult human brain. A non-medullated nerve-fiber on a small blood-vessel (size, 0.1 mm.) ending in a bulb (*B*). (Schultze-Stöhr method. × 540.)

While it cannot be denied that the so-called Rouget cells are present in the larvae of Amphibia, they were not found in the adult Amphibia or in mammals, though Krogh (12, 13) states, somewhat vaguely, that they were found also in mammals (in the connective tissue and in the blood-vessels of the skin). Even in the larvae, however, these cells are not muscular, but mesenchymal, as has been, in the author's

opinion, conclusively proven by E. R. and E. L. Clark (4). One may see such cells in the capillaries of any brain, including that of man. Figure 106, for instance, shows a minute capillary, just wide enough to harbor one red blood-corpuscle. The lumen of the capillary exhibits at *E-E*, thin, flattened, endothelial cells. Outside the lumen, over the endothelial membrane, a different type of nucleus—peri-endo-

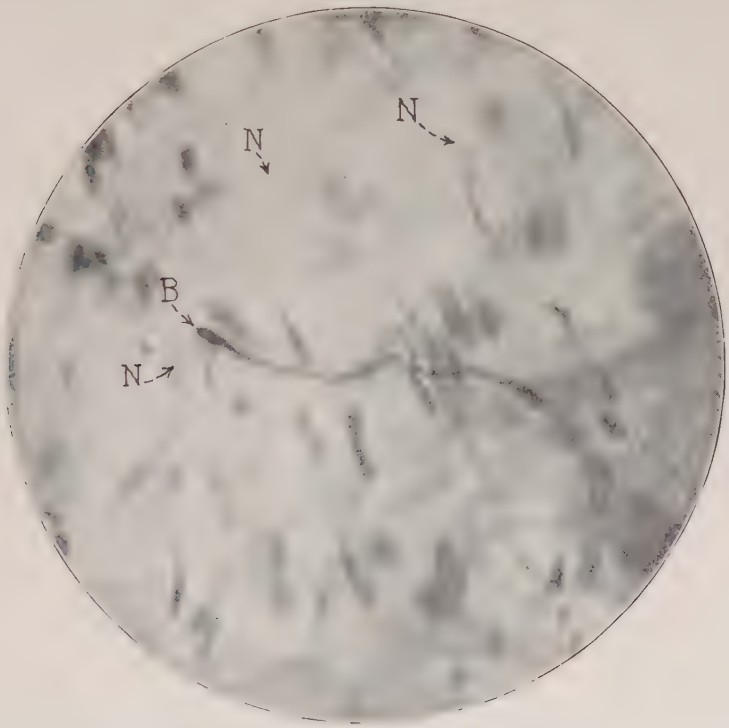

FIG. 105. Several nerve-fibers (*NNN*) of the muscularis; one exhibits a terminal bulb (*B*). (Schultze-Stöhr silver stain. × 640.)

thelial—is present (at *R*). It is larger and enveloped by thin processes (*M*). Its aspect and position correspond exactly to what S. Mayer (17) and especially Vimtrup (38) described as Rouget cells which, as pointed out, constitute in their opinion the muscular apparatus of the vascular capillary system. The absence here (Fig. 106) of the processes which are usually abundant in Rouget cells, may be due to the time element, for, as Clark and Clark (3) showed, the "branched

processes of the stellate connective-tissue cells are gradually withdrawn as its protoplasm flattens out on the endothelial tube. It remains permanently flattened out on the outer wall of the capillary, definitely distinguishable from its endothelium."

Even assuming that the cells in question are muscle-cells, their anatomic connection with the nerve-fibers would be altogether incon-

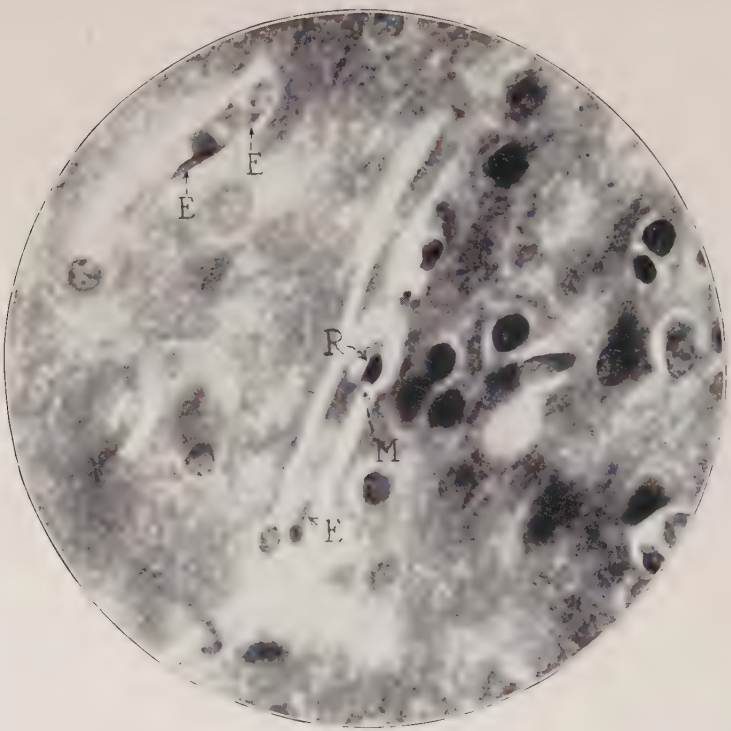

Fig. 106. A capillary. At *EEE*, endothelial cells; at *R*, a so-called Rouget, peri-endothelial or adventitial cell, enveloped by its processes (*M*). (Alzheimer-Mann stain. × 600.)

ceivable. The entire length of the adventitia (Fig. 107) of the capillary is taken up by, or covered with, the footlets of the macroglia (cytoplasmic and fibrous glia). Were the capillaries supplied with nerve-fibers, these would not even reach the adventitia, but would end in the peri-adventitial glia. The space separating the latter from the adventitia is generally considered an artifact, and is also described as

the "shrinking space" or as the space of His. In the picture it is traversed by numerous threads connecting the adventitia with the surrounding parenchyma. Were the wells of the capillary supplied with nerve-fibers, the latter would be seen traversing the periadventitial spaces. This is not the case, however, for the foregoing threads

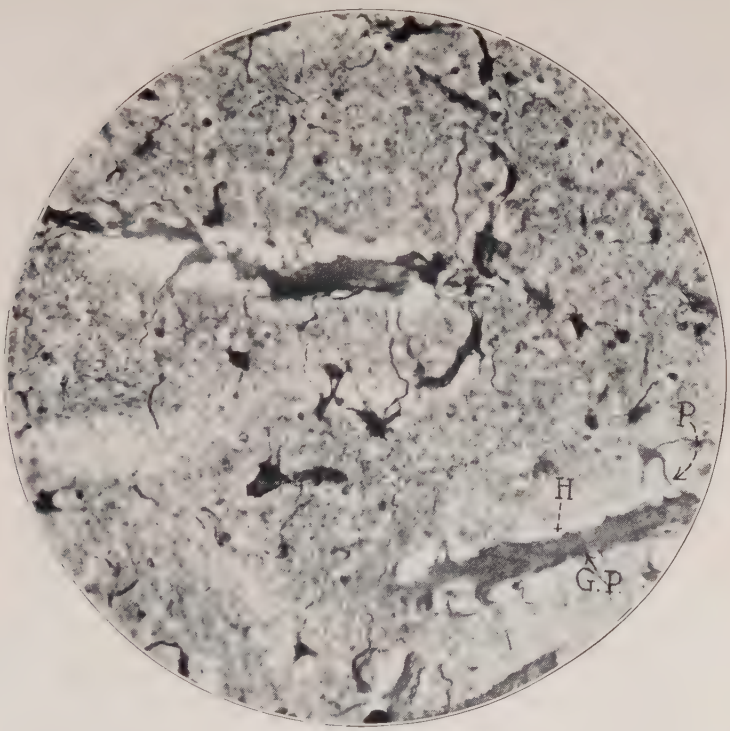

FIG. 107. A capillary. The processes of macroglia cells (*P*) are seen attached to and extending at (*GP*) along the adventitia of a capillary. As thin fibrils they bridge the space (*H*) between the adventitia and the parenchyma (at *P*). No other formations such as nerve-fibers can be detected. (Cajal gold corrosive sublimate stain. × 380.)

are parts of the glia processes. It is probable that such footlets have been mistaken by Hunter (10) and others for ganglion-cell processes which, in their opinion, innervate the cerebral blood-vessels.

It was also suggested that the nerve-fibers after leaving the pia or branching off from the larger nerves of the pia, merely run along be-

side the capillaries, accompanying them. Such an assumption is altogether illogical, mainly because of the enormous masses of capillary blood-vessels in the brain (Fig. 108). Here the capillary networks are

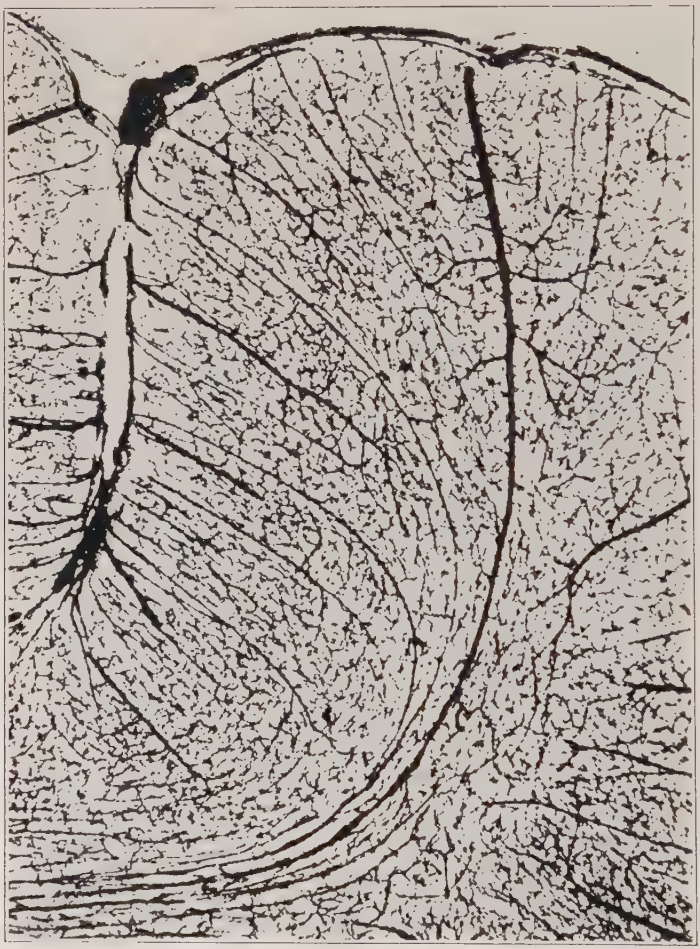

Fig. 108. Vascular supply of a cortical area (from Pfeifer (22)).

denser than elsewhere in the body (Lorente de Nó (16)), the meshes being just large enough to make room for one ganglion-cell, while, according to Krogh (12, 13), in a small mammal, 1 sq. mm. harbors more than

4,000 capillaries. If the capillaries possess nerve-fibers at all, they must be derived from the nerves of the pia. As these are themselves microscopically small, though very abundant, they would be decidedly insufficient to provide myriads of capillaries and other blood-vessels of the brain with even the tinest threads. It is evident that capillary innervation is an anatomical impossibility. Physiologically it is not necessary, for Roy and Graham Brown (27), Roy and Sherrington (28), Bayliss and Hill (1), Langley (14), and others have shown that the contraction of the capillaries may be brought about by chemical and other factors. Recently, for instance, Nesterow (19) has pointed out that the innervation and activity of the precapillary arteries, which are under the constant control of the central nervous system, are sufficient to explain the phenomena which characterize the capillary blood circulation, and that the active contraction of the capillary walls is unnecessary. Of a somewhat similar opinion is Ohno (21). Some writers, as for example, Rohnstein (24), go so far as to deny altogether the existence of nerve-fibers even on the walls of the larger blood-vessels of the pia, while other investigators, such as E. Weber (39, 40), Lorente de Nó (16), hold that the blood circulation may partly be regulated by the glia cells through their processes which are attached to the adventitia. It would thus seem reasonable to agree with the physiologists (Bayliss and Hill (1), Roy and Sherrington (28)), that the cerebral blood-vessels proper do not possess nerves. Nerves, however, are abundant in the pial blood-vessels which not only supply their cerebral branches with blood but seemingly also control, indirectly, their activity.

CONCLUSIONS

1. The blood-vessels of the pia are rich in nerve-fibers.
2. The vascular nerve-fibers may be single, or in bundles; they are mostly naked, that is, devoid of a myelin cover.
3. The blood-vessels of the cerebral parenchyma, as well as the pial capillaries, are devoid of nerve-fibers.
4. The nerve-fibers are especially abundant at the base of the brain, where they are mixed with chromatophores.
5. The pia dominates the cerebral circulation not only by supplying the vessels with blood, but also, partly at least, by controlling their activity (contraction and dilatation).
6. The cells of the adventitia of the cerebral capillaries are practi-

cally identical with the so-called Rouget cells. These are not muscle, but connective-tissue cells, and have nothing to do with capillary innervation.

DISCUSSION

The following questions submitted to Dr. Hassin before the Commission, together with the answers to them, are here reported verbatim.

Dr. Huber: Mr. Chairman, I should like to ask Dr. Hassin, whether, in his preparations made by Schultze's silver method, he was able to differentiate clearly between the endings of afferent nerve-fibers and the efferent motor fibers. In 1899 I reported on observations (9) made on the nerve-fibers in connection with the intracranial vessels using the intravitam methylene-blue method. It was possible to use large pieces of the pia mater and trace small bundles of nerve-fibers for long distances. Certain of the nerve-fibers observed, were found to be sensory nerve-fibers coursing with the sympathetic fibers; sensory fibers having a diameter of 5μ to 6μ and terminating in free sensory endings. The preparations of Dr. Hassin's, judging from the figures presented, are very convincing and help to confirm the view that the intracranial vessels possess vasomotor fibers. It is quite clear that the intracranial vessels possess endings of both afferent sensory nerve-fibers and efferent motor fibers.

Dr. Hassin: No, it is impossible to make a dfferential diagnosis between afferent and efferent motor fibers by this method.

Dr. Spiller: I understand that when a vessel is tied or cut during an operation, and the patient is under local anesthesia, a sensation of pain is produced. This may be explained by the nerve-fibers that you have described. Are you able to conclude from your findings that sympathetic fibers may conduct sensation, and that this sensation is merely one of pain?

Dr. Hassin: It is presumed that the medullated fibers found in the adventitia with bulb-like endings, are sensory fibers, while the non-medullated fibers are sympathetic. That is assumed by the majority of the investigators, but it is, of course, impossible to state whether the sensation of touch or any other sensations, except pain, are conducted by vascular nerves. I do not know what kind of sensation the vessels have. It is just admitted that there is some pain when the blood-vessel is ligated and that pain is caused by the presence of these sensory nerve-fibers, but I do not know what other kind of sensation they might conduct. In fact, I did not pay much attention to the physiological aspect of this investigation. I centred my efforts on the histological part.

Dr. Cobb: If I understand rightly, Dr. Hassin's main thesis is this: that there is innervation of these blood-vessels of the arachnoid space and pia; but that after they penetrate into the brain substance and spread out and anastomose, they do not have any innervation. That (as I will bring out in my own paper which follows immediately after this) really co-ordinates very nicely with my observation.

On the other hand, Dr. Hassin states that there is an enormous amount of vascularity in the brain cortex and that it is really practically impossible, because of lack of space, for enough nerve-fibers to pass to all of these blood-vessels. This I do not believe, because I have made capillary counts on the cortex and learned from these that in 1 cmm. there are about 1000 mm., in length, of capillary. There are, on the other hand, in the heart-muscle in the same amount of space, 11,000 mm. in length; in ordinary skeletal muscle, if it is active, about 6000, and at best about 2000. These, I deduce from the work of Krogh (12, 13). Therefore, these blood-vessels here are using up something like 68 per cent of the available space and there is plenty of room for the innervation. In your splendid histological work you have not found any nerves, and I accept that, only the argument that there is not room enough for nerve-fibers, I would contravert.

I think almost everything else in this discussion we can leave until after my paper, because mine brings out evidence as to the way in which these fibers may work.

Dr. Hassin: In answer to Dr. Cobb, I did not mean to say that there is not enough room in the brain for the nerve-fibers. What I meant to say is that the adventitia of a cerebral capillary is covered by the processes or footlets of the cytoplasmic or fibrous glia. The glial process being above the adventitia would be the place of landing of the nerve-fibers if the cerebral vessels possessed such. There is no room for them in the walls of the blood-vessels. It was surely my fault for not making it clear.

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CHAPTER XX

THE CEREBRAL CIRCULATION

The Relationship of the Cervical Sympathetic Nerves to the Cerebral Blood-Supply[1]

STANLEY COBB, M.D.

INTRODUCTION

FOR more than thirty years there has been a controversy as to whether or not cerebral vessels are under vasomotor control. The present paper is an attempt to indicate briefly the history of the subject and to report in a summary way some recent work from the Department of Neuropathology at the Harvard Medical School.

The standard text-books on physiology in English give the impression that the question is settled; that there is no such control, and, in fact, that there are no nerves to the vessels of the brain. For example, Bayliss (1) states: "As will be seen later, there is no adequate evidence that the cerebral vessels have any vasomotor control; the importance of the brain is such that its circulation is regulated by the whole of the rest of the body, which is caused to accommodate itself, by constrictor and dilator nerves, to the needs of the brain." On the other hand, clinicians have long accepted "cerebral vascular spasm" as the cause of transient hemiplegia, aphasia, migraine and convulsion.[2] For example, the following statement is found in Cecil's "Text-book of Medicine" (3): "There have been reported cases of transitory hemiplegia resulting from *cerebral vascular spasm.* The condition is allied to intermittent claudication of the lower extremities. These 'vascular crises,' as they have been termed by Pal (14), are particularly common in smokers."

The physiological dogma that the cerebral vessels lack all vasomotor control seems to have its origin in the work of Leonard Hill (10). Hill's experiments led him to conclude that in every experi-

[1] From the Department of Neuropathology, Harvard Medical School. The present study is No. IX in a series of papers on the cerebral circulation.

[2] For a detailed discussion, see Lennox and Cobb (12).

mental condition the cerebral circulation passively follows the changes in the general arterial and venous pressures, and that there is no evidence for the causation of cerebral anemia by spasm of the cerebral arteries. These sweeping conclusions have been accepted without critical examination by the writers of most text-books. The work of Weber (21) does not appear to have been read by many English-speaking physiologists. Experimenting with cats, he found in 75 per cent a decrease in brain-volume following the stimulation of the cervical sympathetic nerves. He criticised Hill's method because it did not take into account changes in pressure due to an increase in the amount of cerebrospinal fluid, a factor which might well mask the effects of vascular change as determined by Hill. He, therefore, considered Hill's method inadequate and his conclusions false. Weber's work, though excellently done, gives only indirect evidence. The vessels of the brain were not actually seen to change in caliber; he argued that they must contract and dilate because brain-volume changed and all other variables were controlled.

Müller and Siebeck (13) carried out experiments which indicated that there was a distinct and fairly rapid increase in the volume of the brain after the section of the cervical sympathetic nerve, the systemic blood-pressure remaining at a constant level. Hürthle (11) and others in his time measured the pressure in the circle of Willis. The stimulation of the cervical sympathetic nerves caused an increased arterial pressure synchronous with a drop in jugular venous pressure. For a comprehensive bibliography, the reader is referred to Tigerstedt's "Physiologie des Kreislaufes" (20) and to the recent paper by Forbes and Wolff (7).

RECENT EXPERIMENTAL WORK

Indirect Observations

A series of experiments by Talbott, Wolff and Cobb (19) may be briefly reported here. Ten cats were operated upon under ether anesthesia. In each the left cervical sympathetic nerve was aseptically exposed, cut and approximately 2 cm. removed. An increase in the temperature of the ear and a constriction of the pupil on the affected side were accepted as evidence that the cervical sympathetic nerve had been cut. After a lapse of time varying from one hour to six days, there was injected into the vessels of the head and brain,

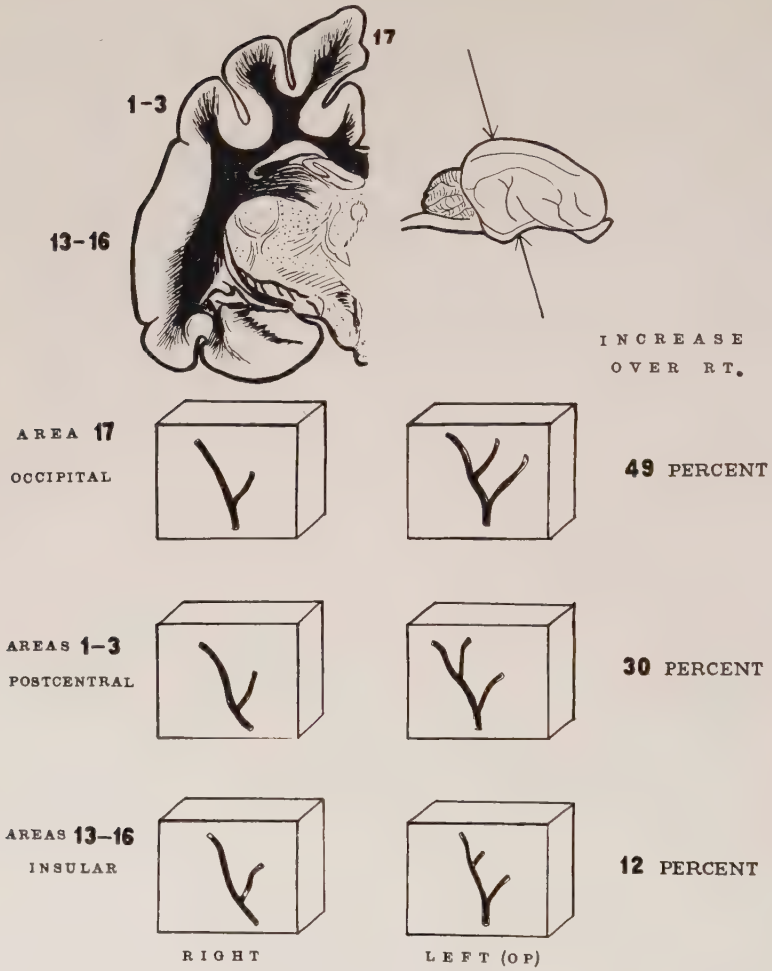

FIG. 109. Diagram showing the increase in capillary bed in the left hemisphere after left cervical sympathectomy. Each block represents 100,000c.μ of cortical tissue, the blood-vessel drawn in represents the length of injected capillary measured in this block (about 62μ in length, in the normal right hemisphere). After cutting the left cervical sympathetic nerve there is found by micrometry of the injected capillaries an increase of from 12 to 49 per cent in the capillary bed in the left hemisphere. The arrows indicate the plane and level of section of the cat's brain. The sketch of the section at the left shows the location from which each of the three blocks of cortex was removed for microscopic examination.

a 2 per cent aqueous solution of Berlin-blue. The injection method is briefly as follows:

After anesthetization with ether the thorax was rapidly opened and the heart and great vessels were exposed. The internal mammary arteries and the abdominal aorta were clamped. The pericardial sac was next opened and an incision was made through the wall of the left ventricle. A cannula was inserted through the incision and carried past the aortic valves into the ascending aorta and ligatured. The injection-mass, warmed to body temperature, was then allowed to run in at a constant pressure, varying between 220 and 225 mm. of mercury. Ludwig's injection apparatus was used. With this apparatus the injection-pressure was recorded and controlled throughout each experiment. The amount of Berlin-blue injected into each animal varied between 150 and 200 cc. The injection was started while the animal was still alive, but within five to ten seconds the animal was dead. Speed is an important factor because even a brief delay would allow asphyxia to dilate the vessels. After the injection the brains were hardened, embedded and cut. Serial sections were made from a block of sufficient size to include the whole surface of the brain at the level indicated in Figure 109. In these sections micrometer measurements were made of the injected capillaries in the *Area occipitalis* (Area 17 of Winkler and Potter (23)) in the *Area postcentralis* (Areas 1–3) and in the *Area insularis* (Areas 13–16). Knowing the area covered by the square micrometer scale, and the thickness of the section, the length of the injected capillary per cubic volume of brain-substance could be measured with approximate accuracy for each hemisphere. Technical errors such as those due to the shrinkage in fixation become insignificant when only comparative measurements of the right and left hemispheres are used. As the left cervical sympathetic nerve was cut in each case, the left hemisphere was considered as the one experimented upon, and the right hemisphere was taken as the control.

Good preparations with even injections were obtained in eight of the ten animals. The capillary measurements showed that in every case more capillaries were open on the side operated upon (left hemisphere) than in the normal right hemisphere. The greatest increase was in the *Area occipitalis*, it was distinct but less marked in the *Area postcentralis*, and very slight or negligible in the *Area insularis*. According to Stöhr (18) there are several routes by which cerebral vasomotor nerves reach the brain, it is unlikely therefore that cutting the cervical sympathetic nerve on one side will completely denervate the ipsolateral hemisphere. This may account for the variations observed.

Taking all the observations and averaging them, a comparison of the side operated upon (left hemisphere) with the unaffected side (right hemisphere) shows that in the *Area occipitalis* there was an increase of 49 per cent in the length of the injected capillary, in the *Area postcentralis* an increase of 30 per cent, and in the *Area insularis* an increase of only 12 per cent. The latter figure is within the limits of probable error and means little. The other two are significant, especially because the two most important sources of error both tend to dilate capillaries and thus make less obvious the difference between the affected and normal sides. These sources of error are (*a*) the unavoidable period of asphyxia at death, (*b*) the injection under a pressure of 220 mm. of mercury. Thus the conclusion appears justifiable

that cutting the cervical sympathetic nerve causes an increase in the capillary bed of the ipsolateral cerebral hemisphere.

Direct Observations

All the experiments so far described are indirect and are therefore not entirely satisfactory, but there is a group of investigators who have observed directly the cerebral circulation through a trephine

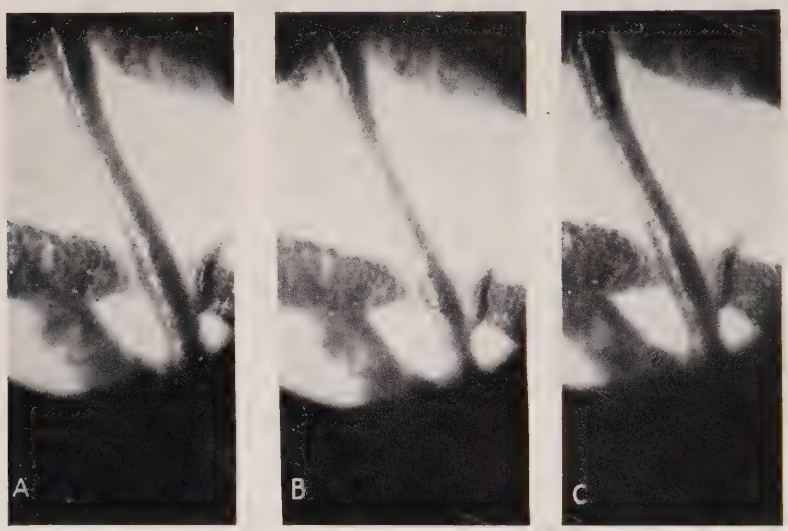

FIG. 110. Microphotographs of a pial artery taken through a window in the skull of a cat. *A*, two minutes before sympathetic stimulation. The artery is 58μ in diameter. *B*, forty seconds after a sixty-second faradic stimulation of the left cervical sympathetic nerve (coil distance 9 cm.). The artery shows a constriction amounting to 15 per cent of its initial diameter. *C*, at the end of a sixty-second faradic stimulation of the left vagus nerve (coil distance 9 cm.). The artery has dilated to 63μ in diameter, which is 7 per cent larger than before the sympathetic stimulation.

hole in the skull. Since the time of Brachet (2) numerous authors have made microscopic observations of the living cerebral vessels and have seen changes in the caliber of the vessels after stimulation. Their work, however, was done with an open skull, a procedure which so greatly alters the relationships of intracranial pressure that conclusions drawn from these observations cannot be used as proof for or

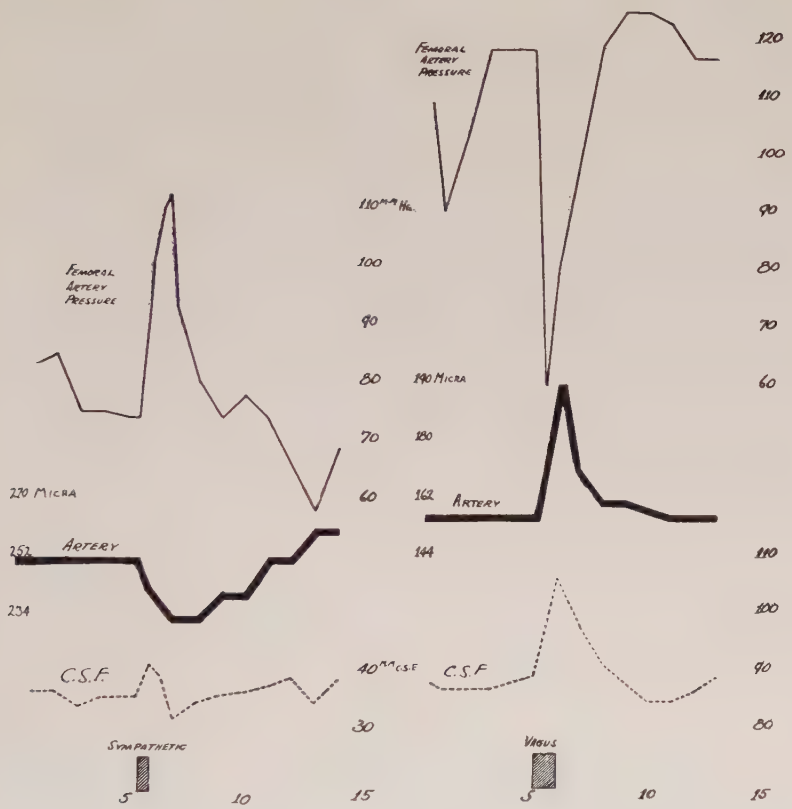

Fig. 111. Two experiments by Forbes and Wolff showing the effects of (*a*) sympathetic and (*b*) vagal stimulation. Time is given as the abscissae in minutes. Faradic stimulation was applied to the nerves in the neck during the time covered by the shaded quadrangles. The lower dotted line gives the intracranial pressure measured in millimeters of cerebrospinal fluid registering in a manometer attached to a needle in the cisterna magna. The heavy middle line shows the changes in the diameter of the pial artery as measured under the microscope in micra. The upper line shows the variations in femoral artery pressure measured in millimeters of mercury. It is obvious that the changes in caliber of the pial artery are not only independent of, but in spite of, the changes in the systemic arterial pressure. (For other experiments and details, see Forbes and Wolff (7)).

against normal vasomotor control of cerebral circulation. It is, of course, agreed that their investigations are valuable in other directions.

A window in the skull was first introduced by Ravina in 1811 (16). In 1902 Cushing (4) employed it to watch the effects of increased intracranial pressure. More recently Forbes (6) has greatly improved the technique by adding a washout system beneath the window, by applying micrometry and microphotography to the vessels observed, and by concomitantly recording arterial and cerebrospinal fluid pressures. The observations made by Forbes and Wolff (7, 25) bring strong evidence to support the theory of vasomotor control. The pial vessels are seen to contract immediately after the stimulation of the cervical sympathetic nerve and to dilate after the stimulation of the central end of the cut vagus (see Fig. 110). During these reactions the systemic arterial pressure either remains constant or rises during cerebral vasoconstriction and falls during cerebral vasodilatation. Changes in the pressure of the cerebrospinal fluid in general parallel sudden changes in the diameter of the arteries, the pressure rising with dilatation and falling with constriction (see Fig. 111). These observations definitely controvert Hill's statement (10) that the cerebral circulation passively follows changes in the systemic arterial pressure; they also add convincing data to the evidence already contributed by Weber (21), Hürthle (11) and others.

Effects of Adrenalin

In addition to experiments on nerve-stimulation, much work has been done on the effect of adrenalin on the vessels of the brain. The use of this drug, as a method of determining the presence of vasomotor nerves, is not entirely satisfactory, although such an authority as Gaskell (8) states that the action of adrenalin has proved the existence of vasoconstrictor nerves in the brain. Schilf (17) is of the opinion that the action of adrenalin in itself cannot be used as a proof of the presence of vasoconstrictor nerves. Such interesting work as that of Wiggers (22), who showed by the perfusion of an excised brain that adrenalin decreased the outflow, should only be used as corroborative evidence of the existence of vasomotor nerves. The recent experiments of Gruber and Roberts (9) explain the former conflicting evidence in this field; apparently the dilatation of cerebral vessels following the application of adrenalin recorded by several observers, was due to the use of acid solutions, or to chloretone. Pure adrenalin alkaloid causes vasoconstriction if the solution is not acid.

Thus there is good evidence that the cerebral vessels contract on the stimulation of the cervical sympathetic nerve, that they lose their tone and dilate when that nerve is cut, and that they dilate when the central end of the vagus nerve is stimulated. In other words, the blood-vessels of the brain react in the same way as do the vessels of other organs. It may well be that they react less strongly. Forbes and Wolff (7) observed in the small pial arterioles an average reduction of diameter of only 8.5 per cent on sympathetic stimulation, and a dilatation on vagal stimulation averaging 22 per cent of the diameter. From the functional standpoint, however, this is far from an insignificant change, for according to Poiseuillé's law (15) the minute-volume flow through a capillary tube of given length varies directly with the fourth power of the diameter of the tube. With a 22 per cent increase in diameter, therefore, there would be an almost 150 per cent increase in blood-flow, that is the minute-volume would become two and one-half times as great.

CONCLUSIONS

Taking all this evidence into consideration it would seem that vasomotor control of at least the superficial cerebral vessels is now established. One must be guarded, however, in drawing clinical conclusions. Physiologically it has been shown that pial vessels may constrict or may dilate in response to appropriate stimulation, but in anesthetized animals the changes are not of great magnitude, and may be overcome by large variations in systemic pressures. Hill's statement, strictly speaking, still holds: "There is no evidence of a causation of cerebral anemia by spasm of the cerebral arteries." Real, obliterating angiospasm has only been experimentally observed when vessels are strongly and locally stimulated under non-physiological conditions—Florey (5), Wolff (24), Lennox and Cobb (12). Recent investigations, however, certainly make vascular spasm a much more reasonable working hypothesis than it was thirty years ago.

DISCUSSION

The following questions submitted to Dr. Cobb before the Commission, together with the answers to them, are here reported verbatim.

Dr. Sachs: Mr. President, I daresay that the importance of all these observations is enhanced by the bearing that they have upon clinical facts.

I was very much struck by Dr. Cobb's statement that, if I understood him correctly, the laws of sympathetic innervation were entirely opposite as applied to the brain or to the blood-vessels of the brain and as applied to the blood-vessels in other parts of the body. If that is correct, I should like to know what his idea is as to where this sympathetic innervation ceases or where the laws become entirely different. Of course, I do not think anyone will deny that there is a distinct sympathetic influence on the brain. Or else, why would a person faint under strong emotion, or under strong fright? Does Dr. Cobb simply mean to imply that after the blood-vessels have once reached the brain the innervation stops or the laws change?

Dr. Cobb: I did not express myself very clearly, I imagine. I meant to say that there was a dogma laid down by the old physiologists that the blood-vessels of the brain were unique and acted in a unique way. My work, I think, indicates exactly the opposite, that they act in the same way as do all the other blood-vessels of the body, and that they are not in the least unique; I believe that we have exploded this dogma that there is anything unique about the brain-vessels.

As to the actual innervation, it accompanies the large arteries and also, according to Stöhr (17), some of the cranial nerves.

I should also like to emphasize that these observations are interesting in relation to clinical cases. We can now much more easily explain "vascular crises," as in transient amblyopias, hemiplegias, and all that sort of thing. These are explainable in exactly the way that Dr. Sachs brought out.

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CHAPTER XXI

VAGUS NERVE ACTIVITY IN RELATION TO THE CARDIAC AND PYLORIC SPHINCTERS; ANIMAL EXPERIMENTATION

WALTER HUGHSON, M.D.

INTRODUCTION

THE difficulty in obtaining clinically useful data from experimentation upon the sympathetic or parasympathetic nerves is nowhere more strikingly shown than in the interpretation of their function in the motor activity of the stomach. Carlson and his co-workers (2) have stated this problem clearly in an article devoted largely to the nerve-control of the cardiac sphincter. This author says that "the visceral nerves are complex association paths connecting cerebrospinal and visceral reflex centres, rather than relatively simple nerves like the skeletal efferents," and further à propos of the subject under discussion he feels that "the prevailing view of antagonistic action of the vagus and splanchnic systems is not tenable for the cardia and the stomach." With much the same idea in mind a series of experiments was undertaken several years ago in the hope that possibly more simple and direct reactions might be demonstrated. The obviously abnormal conditions prevailing in the course of any acute physiologic experiment or one in which elaborate recording devices are employed would seem to vitiate very largely results obtained therefrom, at least insofar as these results may be applied to normal physiology. The effort has therefore been made to avoid as completely as possible arriving at conclusions during the actual performance of the experiment. Another difficulty has been the resistance of most laboratory animals to the production of a chronic pathology in any way analogous to the abnormal conditions in the human being which are responsible for functional disturbances of the alimentary tract. It was thought that any constant effect of a given procedure, however complex the latter, might reasonably be assumed to be at least the outstanding result of the experimental state produced.

Observation had indicated that the gross normal motor physiology

of the dog's stomach was in many respects similar to that found in man. Subsequent clinical application of these laboratory findings has borne out this assumption quite fully. As a consequence dogs have been used in all the experimental work detailed below and appearing in the author's original papers (5, 6). So far as possible animals of a given size, degree of nourishment and general type have been employed. The parts of the alimentary tract under discussion are the pyloric and the cardiac sphincters.

Under the conditions of such experimentation undoubtedly many of the finer details of reaction are lost but on the other hand clear-cut results seem to have been obtained with reasonable consistency.

No attempt will be made here to review the voluminous literature on this complex subject other than to say that all degrees of specificity of function have been assigned to the vagi and sympathetic nerves. There can be, however, no doubt that general experimental conditions, strength of stimulus, the species and conditions of a given animal may modify any and all results obtained. The action of drugs has not been considered in tabulating the results shown below.

EXPERIMENTAL WORK

To establish a standard from which variations might be accurately measured, the activity of the stomach was studied fluoroscopically in a considerable series of dogs not subjected to operation. The conditions of examination in all animals were identical. The regular kennel meal was given at 4:00 p.m. the day before examination, and nothing further by mouth, with the exception of water, until 9:00 o'clock the following morning, when the fluoroscopic studies were begun. The opaque meal, 42 gm. of barium sulphate in 300 cc. of water, was given by means of a stomach tube. The animals soon became accustomed to the passage of the tube and offered little, if any, resistance. The dogs were fluoroscoped unrestrained and lying on their stomachs; incidentally they rapidly became accustomed to the darkness and noises of the X-ray room. Observations were made at intervals of fifteen minutes until the stomach was completely empty. Repeated observations were made on the same animal to control the possibility of daily individual variations. Forty-one complete fluoroscopic studies were made. The average emptying time of the dog's stomach, under the conditions outlined above was 3.4 hours, with low and high extremes of 1.5 and 6 hours.

To effect this normal emptying by some type of chronic irritation, various procedures were carried out in the abdominal cavity under standard surgical conditions. The effect of an anesthetic, the preliminary narcotic, simple laparotomy with its necessary trauma to the peritoneum, all have a fleeting effect but this passes off in the course of a comparatively few hours. Linear incision, and the cautery and closure of the cecum with a conscious effort toward peritoneal trauma, produced the most lasting change upon the gastric motility. The emptying time was increased to an average of 5.7 hours or 2.3 hours above normal. The average total duration of the effect was two weeks, while in two animals the delay in emptying persisted over a period of six weeks. Fluoroscopic examinations were made 24 hours after operation and on subsequent days thereafter. Motility of the stomach as measured by the frequency and strength of contraction waves was carefully noted and found to be unaffected except where a general peritonitis had developed.

With this last fact in mind, an effort was made to demonstrate the relation of the pylorus to this delayed emptying. Accordingly animals whose emptying time had already been established were subjected to carefully performed pylorectomies. Following this type of operation the emptying time was in practically every instance cut at least in half and this effect persisted indefinitely. When, however, the operation described above, linear incision and suture of the cecum, which had never failed to produce delay in emptying in animals with an intact pylorus, was subsequently performed upon this second group, no effect whatever could be observed. It seemed, therefore, reasonable to conclude that under the given experimental conditions prolonged peritoneal irritation remote from the stomach itself, produces a delay in the emptying time as determined by fluoroscopic examination and that this delay was produced largely, if not entirely, by a reflex activity of the pyloric sphincter. Strauss (9) gives convincing clinical support to this assumption.

With these data available, attention was subsequently directed to the rôle of the vagi in this activity of the pylorus. Latarjet (7) has reported an extensive experimental and clinical study on the effect of resection of the nerves of the stomach and has given also a useful anatomic review of the distribution of these nerves. The problem is a complex one for, as Latarjet has stated, "It is not possible to define definitely a nerve distribution (gastric branches of vagi) belonging

only to pneumogastric or exclusively to sympathetics, each gastric nerve having, in proportions of which we are still ignorant, elements pertaining to the two systems. Their limited distribution permits us to say that their section will insure the division of all the extrinsic nerves of the region."

Just above the cardia in the dog the right and left vagus break up to form a plexus completely surrounding the terminal esophagus. Here the vagal plexus is joined by a sympathetic trunk of considerable size. Therefore a pure vagus effect might be expected by division of the vagus branches above this point while a combined effect would result from division lower down. These two procedures were accordingly carried out. In the first place a complete circumcision of the lower end of the esophagus was made to insure division of all vagus fibers above their junction with the sympathetic trunk—this was more easily accomplished by drawing the esophagus down into the abdomen a distance of 1 to 2 cm. The second effect was procured by division of the gastric branches of the vagi just below the lesser curvature on the anterior and posterior stomach-walls. These branches are easily seen and their position was surprisingly constant. They do not actually enter the wall of the stomach for some distance after leaving the lesser curvature. Great pains were taken to avoid injury to any one of the blood-vessels of the stomach-wall.

In thirteen animals both vagi were sectioned at the cardia and following this the average emptying time of the stomach proved to be 2.4 hours, while with division of the gastric branches of the vagi in a similar number of animals the emptying time was 2.5 hours. With both procedures, therefore, the emptying time was reduced approximately one-third and the effect of the sympathetic fibers as distinguished by the two types of nerve-section was apparently negligible. It must be noted that in a few of these animals there remained at the end of the emptying period a very small amount of barium. This could occasionally be seen under the fluoroscope for several hours, and was felt to represent a point in the emptying process beyond which gastric tonus ceased to be efficient. McCrea (8) and his co-workers in a similar study, which the present results largely confirm, felt that this occasional residue which they also observed should be regarded as part of a total delay, and considered that there was only an initial hastening of the emptying time.

Assuming again that the pyloric activity governs the actual empty-

ing of the stomach and that by nerve-section this emptying time had been shortened the operation which with intact nerves and pylorus had never failed to produce delay, was again performed. Protocols of two such experiments follow:

Experiment 1. Young male mongrel (V-s IX); weight, 6 kilos.

1925

Jan. 30: Ether anesthesia. Operation, section of both vagi at cardia.
Feb. 9: Fluoroscopic examination; emptying time—1 hour, 35 minutes.
" 15: Fluoroscopic examination; emptying time—1 hour, 30 minutes.
" 25: Fluoroscopic examination; emptying time—2 hours, 20 minutes.
Mar. 2: Fluoroscopic examination; emptying time—2 hours, 20 minutes.
" 16: Fluoroscopic examination; emptying time—2 hours, 20 minutes. (Slight residue.)
" 23: Fluoroscopic examination; emptying time—2 hours, 30 minutes. (Slight residue.)

Average of foregoing—2 hours, 6 minutes.

" 27: Operation; ether anesthesia; resection of cecum.
Apr. 3: Fluoroscopic examination; emptying time—2 hours.
" 29: Fluoroscopic examination; emptying time—2 hours, 20 minutes.

Average of foregoing—2 hours, 10 minutes.

Experiment 2. Black and tan bull dog, male (V-s III); weight, 5.5 kilos.

1925

Jan. 1: Ether anesthesia. Operation, section of gastric branches of vagi on both anterior and posterior walls of the stomach.
Feb. 2: Fluoroscopic examination; emptying time—2 hours.
" 9: Fluoroscopic examination; emptying time—1 hour, 30 minutes.
" 11: Fluoroscopic examination; emptying time—1 hour, 35 minutes.
" 18: Fluoroscopic examination; emptying time—1 hour, 30 minutes.
" 25: Fluoroscopic examination; emptying time—1 hour, 45 minutes.
Mar. 2: Fluoroscopic examination; emptying time—1 hour, 30 minutes.
Average—1 hour, 38 minutes.
" 4: Operation; ether anesthesia; linear incision of cecum with cautery.
" 6: Fluoroscopic examination; emptying time—1 hour, 40 minutes.
" 16: Fluoroscopic examination; emptying time—1 hour, 45 minutes.
Average—1 hour, 42 minutes.

In these experiments the emptying time was unaffectd, in other words section of the branches of the two vagus nerves has an effect identical with that obtained from a carefully executed pylorectomy. Though the antral and duodenal contractions prevent precipitate emptying they are incompetent to maintain the normal rate of discharge.

Feeling that in certain selected cases the results outlined above warranted clinical application, the procedure has been carried out at operation six times. The operation offers no particular technical difficulties. In man true pylorospasm is a rare condition; it is usually secondary to gross pathology elsewhere, and to attack only the pylorospasm and not the chronic irritative lesion is more than the average surgeon would feel justified in doing. And yet as soon as both procedures are carried out the final result becomes difficult of interpretation. In only two of these six cases has there seemed justification for performing neurotomy of the gastric branches of the vagi alone. In both of these cases clinical relief of long standing symptoms was obtained. Fluoroscopic examination of the stomach after operation supported in every detail the findings of the laboratory experiments. In the other four cases the neurotomy was performed in addition to appendectomies in two, cholecystectomy in the third and release of lower right quadrant adhesions in the fourth. Complete relief from symptoms was obtained in one case, partial relief in two, and none in the fourth. The injection of symptomatology into this already complicated subject can serve no purpose in the present discussion. However, the fact that the X-ray findings support the laboratory evidence is of some value.

In the experimental procedures outlined above no especial attention was paid to the activity of the cardiac sphincter and though section of the vagi above the cardia probably interrupted this particular source of nerve-supply, nothing of sufficient consequence resulted therefrom to draw attention to this anatomically insignificant sphincter muscle. Indeed, Cunningham (3) says that the strengthened circular fibers of the inferior end of the esophagus form a kind of sphincter for this orifice which serves to prevent regurgitation from the stomach under ordinary conditions. Carlson, Boyd and Pearcy (2) state that "to the cardia and the stomach in the dog the vagi serve both as motor and inhibitory nerves, while Carlson and Luckhardt (1) state that "the present data indicate that tonic inhibitory innervation via the vagus nerves plays a rôle in the motor control of the esophagus and cardia." Various authors report temporary spasm, an esophagus and cardia atonic and patulous following vagus section, while still another obtains different results with nerve-section in the neck and in the chest. All results were achieved by careful observers and in the course of acute physiologic experiments. Again, a review

of the literature tends to cloud rather than clear an already obscure situation. Clinically, the cardiac sphincter, so-called, is of importance from the standpoint of the interesting condition referred to as cardiospasm.

In a series of experiments designed to indicate what, if any, relation the vagus might bear to the cardia, the technical problems of surgical approach added greatly to the difficulty of the situation. It was finally decided to carry out, through the left pleural cavity, whatever procedures were indicated. Dogs were again used throughout. Normally an opaque meal introduced into the esophagus through a tube passes into the stomach in a practically uninterrupted stream. Peristaltic waves can be observed but with no particular accentuation at the cardia itself.

Animals were prepared upon whom a bilateral vagus-neurotomy had been performed at a point 3 cm. above the diaphragm. This level was selected in order to avoid the complicating reactions produced by vagus-section above the heart. Fluoroscopic examination of these animals failed to reveal any gross change in the activity of the cardiac end of the esophagus or stomach. Studies were made at intervals of two days to three weeks after the nerve-section had been performed. Loss of vagus effect therefore presented nothing demonstrable under these experimental conditions.

In order to avoid as far as possible the confusing effect of acute experimental phenomena a second group of animals were prepared in whom two delicate insulated copper wires were looped about the left vagus, fixed at a point 1 cm. from the wall of the esophagus itself and brought out through the chest wall at opposite angles of the incision. Two days later the animal so prepared was examined under the fluoroscope, the ends of the wires having previously been attached to an induction coil. On the introduction of barium into the esophagus, stimulation with a weak current was made. No effect at the cardia could be observed, nor was the cardia noticeably affected with increasingly strong stimulation. After a brief latent period the stomach itself went into violent contraction and discharged its contents with great rapidity. At no time was there delay at the cardia until the current had reached such strength as to produce respiratory embarrassment to the animal. Again under stated conditions of experimentation the vagus nerves appear to have no effect upon the so-called cardiac sphincter when stimulated with an electric current of varying

strength. This condition held true even when the stomach and pylorus were in a state of extreme activity due to the stimulation. Hatcher (4) says "that if a reciprocal relation exists between the cardia and the pylorus it is in abeyance during vomiting." The above experimental results fail to indicate the existence of any reciprocal relation so far as vagus nerve-control is concerned, during the passage of material into the stomach.

Unfortunately the position of the sympathetic trunks is such that surgical approach designed for complete division is extremely difficult and can be performed only at the cost of surgical trauma out of proportion to the possible value of the results obtained. In the present investigation, therefore, no studies have been made upon the cardia with reference to the loss of its sympathetic supply.

Though possibly not pertinent to the present discussion an observation of interest has been made as to the effect of stimulation of the left phrenic nerve upon the cardia. The suggestion that the diaphragm may have some rôle in the production of cardiospasm has of course been previously made. Indeed, phrenicotomy has been performed for the relief of this interesting condition. However, the statement that the diaphragm may actually be the major controlling factor of the cardiac orifice has not been observed in reports of experimental studies.

With the left chest opened and the lower third of the esophagus exposed, water was introduced into the anesthetized animal's mouth through a tube. Simultaneously the left phrenic nerve was stimulated and with the resulting contraction of the diaphragm the column of water was held sufficiently long to produce a dilatation of the esophagus to twice its normal size. Without such stimulation, water passes into the stomach so rapidly that practically nothing except a very fleeting contraction wave can be seen. Under direct nerve-stimulation the diaphragm quickly tires and the temporary but effective obstruction disappears as relaxation occurs. With semisolid material in the esophagus, interruption by phrenic stimulation is produced with great ease. Experiments of this general nature are now in progress, designed to produce a chronic dilatation of the lower end of the esophagus. Before definite conclusions can be drawn, however, means to eliminate the necessity of acute experimentation will be devised.

From the above data it is felt that reasonable evidence has been ad-

vanced to indicate that the major extrinsic nerve-control of the pyloric sphincter lies in the vagi. Whatever effect the sympathetic nerves may have on normal pyloric activity, under the experimental conditions herewith pertaining, no gross effect could be determined under direct fluoroscopic examination by their partial elimination. Furthermore, the accuracy of the experimental findings has received support from clinical cases in which the gastric branches of the vagus had been divided for the relief of pylorospasm. It is realized of course, that the analysis of cause and effect, interpreted on the basis of relief of symptoms, is an extremely complicated matter.

In contrast to the striking effect of vagus elimination upon the pylorus, stimulation or division of the vagi failed to affect the activity of the cardiac orifice in any way. Though the method used for stimulation involved the introduction of an extraneous factor—the presence of wire in the chest—it apparently produced no reaction except when actually conducting electric current.

Though naturally less convincing than graphic representation, it is felt that the present method of study gains in value by the elimination of the many complicating conditions present in the acute type of physiologic experimentation. The value of direct observation depends entirely upon the accurate interpretation of the observer and can be controlled only by the confirmation of others. In the present instance such confirmation is already available.

CONCLUSIONS

1. Section of the vagus nerves in dogs either at the cardia or on the anterior and posterior walls of the stomach caused a decrease in the normal emptying time of the stomach under given experimental conditions. The presence or absence of sympathetic fibers in the two types of section had no demonstrable effect.

2. Following section of the vagus trunks or gastric branches of the vagus, it was impossible to produce a reflex pylorospasm by peritoneal irritation, the latter reaction having been found constant in all animals with an intact vagus supply to the stomach.

3. Support has been obtained for the above conclusion by studying the effect of vagus-section in human beings presenting clinical pylorospasm.

4. Section or stimulation of the vagi in the chest 3 cm. above the cardia has no effect whatever upon the discharge of the esophageal contents into the stomach.

DISCUSSION

The following questions submitted to Dr. Hughson before the Commission, together with the answers to them, are here reported verbatim.

Dr. Cannon: I regret very much that I was called away in the early part of the paper so that I did not hear it all.

Many years ago we made observations on animals that had both vagi severed, one in the neck, the other below the recurrent laryngeal nerve, and observed the phenomenon that Dr. Hughson has mentioned, that is, a delay in the discharge of food from the stomach, a delay which can be accounted for not only by a lessened tone of the stomach (characteristic of the animals we observed with the X-ray for several days after the section), but also by a lessened intensity of peristalsis and apparently by a greater contraction of the pyloric sphincter. Associated with this there was a striking loss of tone in the lower esophagus—a loss of tone which resulted in material's being retained there for a considerable period, and sometimes regurgitated without passing through the cardiac sphincter into the stomach. Although food could be carried through the upper part of the esophagus by swallowing—naturally peristalsis was retained in that part still managed by the superior esophageal branch of the vagus—there was a part below the heart which was denervated and baggy. In the cat, the lower part of the esophagus, from about the heart-level down, is provided with smooth muscle; that gradually regained its tone and when material got into this region there was an intrinsic activity which resulted in pressing the food through the cardiac sphincter into the stomach.

It is a matter of very considerable interest, I think, to neurologists that the vagus has an inhibitory influence on the cardia and on the cardiac end of the stomach when swallowing occurs. It is possible to observe, by means of physiological technique and the X-ray method, peristalsis as it goes on in the stomach in the course of digestion. If, now, material is swallowed, peristalsis ceases; the pressure in the stomach falls from about 15 mm. of water down to zero, and the lowest pressure is reached when the material which is coming through the esophagus arrives at the stomach. Here, in the viscera, is a beautiful example of reciprocal innervation of antagonistic muscles. Just as the triceps relaxes when I contract my biceps, so here, the stomach fibers which are active and producing pressure, are made to relax when the esophagus is pushing material into the stomach. The walls of the esophagus do not have to do work against the pressure which is existing in the stomach. This phenomenon, I may say, disappears if the vagi are cut.

Dr. Hughson: If I understood Dr. Cannon correctly, he felt that I had stated that after division of the vagi in the dog there was a delay in the emptying time of the stomach.

Dr. Cannon: I understood you to say that when you stimulated the vagus there was a faster movement of material out of the stomach.

Dr. Hughson: Peristalsis is more active, but following a division of the vagi, the total emptying time of the stomach is shortened.

Dr. Cannon: Then the condition is different from that in the cat. Immediately after section of the vagus in the cat, there is a delay in emptying time. Indeed, for several days after section of the vagi, I have seen food delayed in the stomach.

Dr. Hughson: In dogs, this occurs immediately, but within twenty-four hours after the operation there is a shortening of the emptying time.

I neglected to mention one factor which is of interest in regard to the tone of the stomach as affected by the vagus. These observations of mine are analagous to those of McCrea and McSwiney (8). They felt that the initial emptying time of the stomach only was increased and that following that there was a relaxation of the stomach and a total delay in emptying time.

I have interpreted this finding a little differently because in our animals (dogs) and in the human beings upon whom I have operated there is at the end of the emptying period a very small amount of barium left in the stomach, which is insignificant so far as the total emptying is concerned, but which I interpreted on the basis of a slight decrease in the tone of the stomach.

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Section V

CLINICAL INVESTIGATION

CHAPTER XXII

SOME REFLEXES OF THE VEGETATIVE NERVOUS SYSTEM WITH REFERENCE TO THE GASTRO-INTESTINAL TRACT

CLARENCE A. PATTEN, M.D.

INTRODUCTION

KNOWLEDGE concerning the functions of the vegetative nervous system in relation to the gastro-intestinal tract, has been difficult to acquire because of the uncertainty regarding the distribution of the vegetative nerve-fibers, the relationship between the sympathetic and parasympathetic systems and the inadequate correlation between clinical phenomena and experimental investigation. The experimental physiologists and the anatomists have contributed much more to the subject than have the clinicians, but all of the experimental work has necessarily been carried out on animals, a fact which has permitted observation of only limited objective phenomena. There is, therefore, a distinct need of a group-study of the vegetative nervous system by the internist, neurologist, physiologist, anatomist and biochemist.

There has been, *pari passu*, a great deal of discussion regarding sensation in the vegetative nervous system, and exact information on this phase of vegetative neurology would possibly clear up many of the more obscure and baffling clinical syndromes. That there are fibers which convey pain impulses, seems certain; but anatomically the pathways have not been definitely defined. The elucidation of this problem would mark a decided advance in neurological knowledge, and should engage the attention of every physician. The consideration of the pain-sense in relation to gastro-intestinal function and disturbance, is the main issue in this contribution.

From a physiological standpoint it seems pretty well established that vegetative function is entirely reflex in character. Normally it is carried on without reference to the will, and enters into consciousness only when a pathological condition exists. Reflex function in this system is probably analogous to the same function in the cere-

brospinal system, and yet it must be conceded that vegetative reflexes are much more complex than the somatic, and almost defy actual elucidation.

There must be a massive system of reflexes, small arcs functioning more or less independently,—for example, the axone-reflex of Langley (12); larger arcs subserving only a limited field,—the myenteric plexus reflexes; and very much larger arcs, integrating the functions of a whole system. There are reflex arcs in the sympathetic system, arcs in the parasympathetic system, and arcs which unite the activities in both systems. In addition there are reflex pathways which must utilize the cerebrospinal system as one arm of the arc, or connect two portions of a sympathetic arc. Just what the anatomical pathways are, cannot be accurately determined insofar as the vegetative-somatic connections are concerned, but it has been definitely established that a functional union exists between the vegetative and the cerebrospinal system. Ranson (20) states that the function of the afferent sympathetic fibers is "to convey to the central nervous system impulses giving rise to vague sensations and other impulses, which never rising into consciousness, give rise to visceral reflexes." So far as reflex function is concerned it is clear that afferent sensory impulses are necessary, but so far as conscious sensation is concerned there is much dispute.

It may be stated theoretically that visceral sensation rises into the field of consciousness only when it is for the interests of the organism to have some knowledge as to visceral activity. For example, the demand on the part of the system for food for the tissue-cells, is indicated by a "feeling" of hunger which is at first more or less constitutional or "all over"; but later if the demands are not met, a sharp, indescribable pain appears in the epigastrium, which is interpreted by the individual as an empty stomach demanding to be filled. When the stomach has been filled to capacity the individual realizes a sensation of "fullness" which is interpreted as a command to eat no more. Parenthetically the latter sensation is pleasurable and painless and is totally opposed to the sensation of emptiness. These are certainly protective mechanisms and are recognized as normal sensation. To trace definitely the sensory pathways subserving such normal sensation, is certainly impossible, but theoretically, at least so far as hunger is concerned, there must be a massive reflex with cerebrospinal components as an integral part of vegetative function.

Kuntz (10) in his work on the development of the sympathetic nerves states that "the existence of sympathetic sensory neurones in the sympathetic trunks and the prevertebral plexuses has not been demonstrated; experimental evidence, however, indicates the presence of sympathetic sensory neurones in the sympathetic plexuses in the walls of the digestive tube. While it is impossible by direct observation to trace either sympathetic excitatory or sympathetic sensory elements back to their specific source in the cerebrospinal nervous system, indirect embryological and anatomical evidence warrants the conclusion that the sympathetic excitatory neurones arise from cells which migrate from the neural tube along the fibers of the motor nerve-roots, while the sympathetic sensory neurones, wherever such neurones exist, arise from cells which migrate from the cerebrospinal ganglia. This interpretation makes the sympathetic neurones homologous with the afferent and efferent components of the other functional divisions of the peripheral nervous system."

There seems little doubt, from the work of various investigators, but that the sensory fibers pass up the spinal cord in or near the anterolateral tracts to the higher centres. Spiegel (25) has definitely committed himself to this viewpoint, and has diagrammatically illustrated the probable pathways.

So far as the sensation of pain is concerned, Langley (13) has expressed the opinion that the higher threshold for pain in the visceral nerves is due to their paucity in a given area, but he also considered the further possibility of the interposition of a cell in the pathway which might raise the threshold. Certain it is, that no matter by what pathway the impulses are conducted, pain or discomfort is recognized only when a certain quality of stimulation has reached a definite point of intensity. Furthermore, it is well known and generally agreed that the only conditions which actually produce pain in the gastro-intestinal tract, are the overdistension or overcontraction of the viscera. Surgeons, gastro-enterologists and experimentalists have conclusively demonstrated that the hollow viscera may be cut, pinched, burned or otherwise traumatized without giving rise to sensation of any sort. The problem, therefore, of the sensory component of the vegetative reflexes in the gastro-intestinal tract, from the clinical standpoint, narrows down to the question of muscle-sensibility, and to the anatomical relationship of the sympathetic and parasympathetic fibers to muscle-function.

From a functional standpoint the parasympathetic fibers apparently perform an excitatory and the sympathetic fibers an inhibitory function on the muscle-action of the gastro-intestinal tract, with the exception of sphincteric control. The myenteric plexus, as pointed out by Cannon (3), seems to be perfectly capable of carrying on gastro-intestinal activity without aid from either the sympathetic or the parasympathetic system. The question then arises as to the purpose of the craniosacral and thoracicolumbar systems of control. The answer is not forthcoming, perhaps, but theoretically it may be stated that they are protective mechanisms,—they act as watchful guardians ready to step in when the myenteric plexus function fails or sends out some signal of distress.

LOCALIZED PAIN

Among other evidences of vegetative nervous system activity, pain is the most important symptom of disturbance. In all clinical work the evaluation of pain as a symptom is of paramount importance, and the question of the interpretation of pain or tenderness arising in a viscus, has been discussed at length by innumerable workers. The difficulty attending the exact localization of pain seems to lie in a differentiation between that which may be confined to and felt only at the site of the lesion and that which may be referred to the body-wall through a corresponding viscero-somatic segment, or that which occurs at a great distance from the organ affected. For the present the discussion will be confined to localized pain in the viscera themselves, and referred pain will be considered later.

The length and position of the gastro-intestinal tract and its relationship to the body, from the standpoint of its nerve-supply, makes difficult the accurate localization and diagnosis of pain. The question of localized pain in any viscus is much discussed, and has an equally large number of proponents and opponents. Regarding the tract according to its natural divisions into esophagus, stomach, small and large intestines, rectum and accessory organs, the subject of localized (and localizable) pain is considered.

The Esophagus

The esophagus is comparatively insensitive so far as ordinary stimuli are concerned, but when any very hot or cold article or alcohol, is placed in the lower end of the esophagus, distinct discomfort is

experienced. Hurst (8) experimentally proved this, and he has been supported by many later authors. He also proved, by inserting inflatable rubber bags and distending them in the esophagus, that any overdistension of the viscus gave rise to a characteristic painful sensation. Not only did the patient experience a painful sensation, but he was also able to point very closely to the area immediately overlying the point of pressure. Many clinicians have noted in cases of organic obstruction of the esophagus that the patient can usually point out the level of the obstruction with considerable accuracy. Hurst states that the afferent fibers bearing these pain impulses are all of vagal origin, and that the sympathetic sensory supply to the esophagus is very small. The normal peristaltic function of the viscus, however, must be similar to that of the rest of the canal; that is, it is carried on by the myenteric plexus, without much contribution from the vagus or sympathetic fibers. Mackenzie (15) vigorously maintains that the only sensations in esophageal conditions are those due to the stimulation of irritable areas in the cord, and are merely referred to the skin overlying the viscus. He denies all organ sensitivity and disregards the assertion of the patients that esophageal pain is felt deeply situated behind the sternum, which is an entirely different sensation from skin hypersensitivity due to local dermal irritation.

The condition described as "cardiospasm" has been much discussed clinically, but it remained for Hurst to point out that the natural state of the lowermost portion of the esophagus is one of tonic closure, and that it opens only to permit the passage of a bolus of food. He describes cardiospasm as a failure of relaxation, and applies the term "achalasia of the cardia." Anatomically the esophagus merges into the cardia of the stomach insensibly, and no true division or sphincter exists between the two structures. Cardiospasm from the gastroenterological viewpoint means a spasmodic contracture of the muscular coat of the lower end of the esophagus and the beginning of the stomach. This muscle is considered to be entirely controlled by the vagus for both opening and closing.

In support of vagus innervation, Spiegel (25) found in autopsied cases of cardiospasm that both vagi were degenerated, and he accounted for the spasm on the basis of an autonomic hyperirritability. Veach (26) found that the vagus had both an excitatory and an inhibitory action upon the esophagus and cardia. Payne and Poulton

(18, 19) have stated their belief in a voluntary control of the cardia, offering as proof the fact that it can be opened at will for belching. On the other hand the author is informed by reliable gastro-enterologists that most people who voluntarily belch, are air-swallowers, and that the act of swollowing produces a peristaltic movement of the esophagus which favors the opening of the cardia and the return of the air. Cannon (4) definitely subscribes to vagus influence in cardiospasm, having found that bilateral vagotomy in the cat caused a temporary paralysis of the lower end of the esophagus with a hypertonicity of the cardia.

The consensus of opinion seems to be that pain sensation in cardiospasm is conveyed by afferent vagal fibers. The parasympathetic pathways are, therefore, concluded to be chiefly responsible for the majority of sensations in this portion of the alimentary canal. So far as localization in the body is concerned, pain in disturbances of the cardia is always "felt" beneath the ensiform.

The Stomach

The stomach has been shown to be insensitive to practically all stimuli except that of alcohol, which furnishes a brief sensation of warmth, according to the experimental observations of Hurst (6). The pain of hunger is due to the rapid and sharply contracting muscles of the stomach-wall, and is localized by the individual in the mid-epigastrium. Spiegel (25) believes that the afferent and efferent fibers are vagal in origin since the stimulation of those nerves causes contraction and increased peristalsis (or spasm) of the body of the stomach. The sensation of warmth following the ingestion of alcohol, Hurst believes, is carried by way of the sympathetic afferent neurones, —a viewpoint decidedly at variance with that of other authors, who consider that the vagal fibers supply the gastric mucosa. According to the latter, in any irritative condition of the mucosa, the afferent impulses must travel by way of the vagus, which, by stimulating the efferent neurones, produces a contraction of the muscles and gives rise to the sensation of pain. The protective mechanism of the vegetative nervous system, on the other hand, might as justifiably be hypothecated as a sympathetic influence arresting overactive peristalsis in mucosal irritation as well as the sensory afferent impulses by way of the sympathetic nerves. Miller (16) agrees with Spiegel that the reflexes caused by irritation of the gastric mucosa are trans-

mitted by the vagus and not by sympathetic fibers. He apparently believes that the vagus fibers end in the muscular coat.

Ranson and Billingsley (21) have found that there is no embryological connection between the sympathetic trunks and the gastrointestinal tract until after vagal migration has been well established. They further state that the myenteric and submucous plexuses are all of vagal origin, and only later in embryonal life is sympathetic relationship effected. It is probable that the vagus and sympathetic systems are developing at the same time, but that the vagal cell-nests which develop along with the gut-tract, heart and lungs, form the basis for the various plexuses, and that in time the cells migrating from the sympathetic trunks and ganglia come into synaptic relation with them.

In most diseases or conditions affecting the stomach, sensation is localized in the epigastric region. When the stomach is full the sensation centres in the midline between the ensiform and umbilicus, but it is not sharply localized,—it is diffuse. This sense of fullness occurs only when pressure by the contents of the stomach is made on incompletely relaxed muscle. Hurst showed that this sensation of fullness is not due to increased intra-abdominal pressure or distension of the abdominal walls from the filled stomach, since the same thing occurs in completely relaxed and loose abdominal walls. The sensation must then arise from the irritation of vegetative nerve-fibers in the stomach-wall.

Hurst (8) stated that in his opinion all true gastric pain was due to abnormally active peristalsis. In cases of gastric ulcer the onset of pain is coincident with the period of the greatest muscular contractions in the territory of the ulcer. Pain in gastric ulcer is apparently not due to irritation of the ulcer by hydrochloric acid, but has been explained as being due to the stimulation of peristaltic activity by the presence of the acid; neutralization of the acid by alkalies consequently removes the excitor of peristalsis, and in this manner relieves the pain. Pain in an ulcer at the cardia is felt just below the xiphoid, and occurs a half-hour after meals,—corresponding to the period of the greatest peristaltic movement in an area where the muscle-fibers are comparatively short. Many ulcers of the body of the stomach are painless, a fact which can perhaps be accounted for on the basis of longer muscle-fibers or of markedly less active muscle-contractions than at the cardia or pylorus. Pyloric ulcer pain is usually noted at the so-called transpyloric plane,

just to the right of the midline—or directly *in* the midline—and occurs from one and one-half to two hours after eating, during the period of the greatest pyloric activity.

According to Bockus (1) an ulcer near the pylorus gives clinically the most definite localizable signs. In the midline of the epigastrium halfway between the xiphoid and umbilicus an area of tenderness about the size of a half-dollar can be palpated. Abdominal-wall tenderness is ruled out by having the patient tense the recti. If no tenderness is demonstrated then, but is found uniformly with the muscles relaxed, it is concluded that the tenderness must be in the ulcer-area in the stomach. Mackenzie (15) believes, however, that all the tenderness is in the spinal nerve-endings just external to the layer of parietal peritoneum, and that the tenderness is referred through the same spinal segment that supplies the organ. Ross (22) subscribes to both viewpoints and is quoted by Hurst as believing that visceral disease may cause true visceral pain, which is often present alone, but which may be associated with referred pain. Hurst is in agreement with this opinion. Lennander (14) agrees with Mackenzie, but Ryle (23) supports Ross and Hurst, stating that "visceral sense is muscle sense," and relief from pain is always brought about by a relief from the muscle-tension. Ryle further believes that visceral pain may be accurately localized by the patient in the absence of somatic pain and tenderness.

The pain of pylorospasm is localized in practically the same region as that of pyloric ulcer. It has been shown that there is no contraction of the so-called pyloric sphincter in this condition, but that the contraction occurs in the muscles of the pyloric antrum. If the anatomists are correct in their statement that the pylorus is opened by the vagus nerves and closed by the sympathetic nerves, then the antrum contraction is possibly due to vagus control, as is alleged to be the case with all the stomach muscles. The opposing action to that of opening the pylorus, i.e. relaxation, is difficult to conceive, except that the vagus nerves might also, as in the cardia, have a double activity. Further speculation concerning the autonomic regulation of this orifice by the myenteric plexus is interesting, but difficult to determine.

In disease of the gall-bladder there is localized tenderness at a point just below the ninth costal cartilage. Pain in gall-bladder disease is definitely analogous to that in the other hollow viscera so

far as its mechanism is concerned, and is due to overcontraction or overdistension of the organ. Its vegetative supply probably comes through both the vagus and sympathetic nerves but the relationship of the various plexuses to its control is not clear.

The Small Intestine

Pain in the small intestine occurs under the same mechanical disturbances of muscles as in the case of the stomach, and is usually localized around the umbilicus, though somewhat diffusely. Tenderness that is not necessarily of somatic origin is greatest near or just below the umbilicus, but is diffused in all directions. In duodenal ulcer the pain begins from two and one-half to three hours after eating and must correspond to the period of the most active peristaltic contractions. It is localized to the left of the midline, while tenderness is sometimes demonstrated somewhat below the transpyloric plane. The taking of food relieves the pain,—a fact that can possibly be explained as due to the removal, in some manner, of the stimulus to peristaltic activity.

Appendiceal pain is subjectively felt near the umbilicus as a rule and somewhat to the right of it, but localizable tenderness will be demonstrated only over the appendix itself—its location varying widely. The pain near the umbilicus is accounted for by some authors on the basis of the embryological development of the appendix in relationship to this area. The well-known clinical fact that in rupture of a diseased appendix all pain disappears shows that pain must be due to the distension of the organ by the retained material. Appendiceal pain is more or less constant but with sharp exacerbations; whereas intestinal pain, such as that in inflammatory or irritative conditions, is griping, colicky and rhythmical, both showing the definite relationship to peristalsis. The severest type of intestinal pain is that due to obstruction.

The Colon

Pain in disturbances of the colon is usually felt in the lower third of the abdomen, although there may be tenderness over the whole of the viscus or any part of it, on deep palpation. There is a functional difference between the proximal and distal portions of the colon, the former having peristaltic and antiperistaltic movements, while the latter resembles the small intestine in having only peristalsis. Whether

or not this difference in function has any bearing upon the character of pain in this region, is not known, but it must be that there is a difference in vegetative nerve-control in the two parts of the colon.

The rectum is insensitive to all stimuli except those arising from contraction or distension. The desire to evacuate the bowels, a normal sensation, is produced by fecal masses entering and distending the rectum. Distension of the rectum, according to Hurst (8) is felt in the lower sacral region posteriorly, while distension of the lower end of the colon is localized near the midline in or near the pubis. Ordinarily the pain that is felt in the anus, which has a somatic sensory supply, comes from a disturbance in the anus, and not from the rectum as is so frequently stated. Rectal pain occurs behind the anus and a little above it.

VISCERO-VISCERAL REFLEXES

The gastro-intestinal tract, because of its size and position is reflexly disturbed by conditions, existing not only within its own territory, but also by disease or disorder which develops in other viscera of the thorax, abdomen or pelvis. In many instances the disease may exist in one place and manifest itself in another location, more or less distant. The diffuse arrangement and remarkable continuity of vegetative nerve-fibers is apparently the explanation for these reflex disturbances. One mechanism which explains these phenomena is the so-called viscero-visceral reflex. A case in point is that of a girl about twenty years of age, who entered the hospital because of intractable vomiting. There were no localizable evidences of disease except from the roentgenological examination, which revealed a tightly contracting band dividing the stomach into two equal portions. This contracture was considered the cause of the vomiting. After a few days of atropine administration, and re-examination by X-ray, the contracting band had relaxed and the stomach appeared normal. The vomiting abated somewhat but returned again, and further search for causes revealed a bilateral salpingitis, which (because of the supposed virginity of the patient) was totally unsuspected. Proper treatment of the tubal infection stopped the vomiting. In this instance the focus of irritation was in the pelvis, but the outstanding manifestations were in the epigastrium.

The pathway for these viscero-visceral reflexes, is not at all clear. Spiegel (24) in a recent article admits a lack of clarity on the

subject, but believes there is verification of some of the possibilities. He states that in part these impulses must run to the posterior nerve-roots, to the posterior horn cells, probably through an interposing or intermediate cell, and then into the cells of origin of the sympathetic nerves in the lateral horn. From these preganglion cells the impulse travels to the sympathetic or prevertebral ganglia by way of the anterior roots, and thence to the viscus. Such an explanation answers perhaps for reflexes where only one or two spinal segments are concerned, but, as in the case cited, the afferent impulses must enter the cord in the sacral region and the efferent impulses pass out from some segment in the thoracic cord, and from the medulla. This is in effect Spiegel's explanation of the mechanism of vomiting. He states that the impulse travels along centripetal fibers, mostly vagus, to the medulla oblongata, ending in the sensory vagus nucleus. From here it passes (*a*) to the motor vagus nucleus by one route, and (*b*) to the nuclei of the substantia reticularis by another route. From the motor vagus nucleus it is transmitted to the stomach by vagal efferent fibers, causing inhibition of the cardial sphincter. From the substantia reticularis nuclei the impulse passes (*a*) by way of efferent fibers to the stomach-wall, causing a contraction of the pars prepylorica and closing the pyloric sphincter; (*b*) by way of the cerebrospinal pathways to the spinal segments of the cord. In the cord the anterior horn cells transmit the impulse to the diaphragm and to the abdominal muscles, causing the contraction of both and the expulsion of the stomach contents. Spiegel's explanation is undoubtedly meritorious and is easily applicable to those organs which are supplied by the vegetative fibers; but there are many other causes for vomiting,—such as severe somatic pain, psychic emotional factors, and the sight or sound of disagreeable and repulsive things. Under these circumstances the impulses arise from varying somatic or cerebrospinal areas, and yet the act is accomplished in the same manner as when the stomach is reflexly affected by abdominal visceral disturbances. Although the pathways are not definite, there is one outstanding fact in this connection, namely, that the whole of the cerebrospinal nervous system and all the peripheral somatic nerves participate in the reflex act. Nature in her prodigality seems to have so designed the entire vegetative system that it functions not only more or less independently, but also with the complementary aid of the somatic nervous system.

That the cerebrospinal system is not entirely necessary in the formation of viscero-visceral reflexes, is proven by the experimentalists who have sectioned the spinal cord and found that certain complex reflex actions take place there. Kehrer (9) accounted for this fact on the basis of the axone-reflex described by Langley (12). As a pure reflex, however, the axone-reflex does not fulfil the reflex requirements of an interposing cell between the afferent and efferent impulse.

Gastric symptoms other than vomiting are notoriously frequent viscero-visceral reflexes. In gall-bladder disease and in inflammation of the appendix or of the pelvic viscera, the reflex symptoms usually encountered are disturbances of gastric secretion and motility and the syndrome called gaseous dyspepsia. Hurst accounts for gaseous dyspepsia by the reflex overproduction of hydrochloric acid, by the inhibition of pyloric relaxation (achalasia of the pylorus) and by gastric hypertonus. Cannon and Murphy (5) produced pylorospasm experimentally by traumatizing the intestines, and they emphasized the fact that in pylorospasm it is the antrum of the pylorus that is contracted and not the pyloric sphincter. As in the case cited by the author, the reflex gastric symptoms continue as long as the focus of irritation remains.

There is one more theoretical consideration for the causation of viscero-visceral reflexes that might be mentioned before leaving the subject. It is the possibility that a stimulus arising in any portion of the sympathetic system may be diffused over a wide area. This theory is based on the possibility that the vegetative fibers through the rich plexus formations in the thoracic abdominal and pelvic cavities are in reality a massive network without any particularly close definition of boundaries and pathways.

VISCERO-SENSORY REFLEXES

In many instances of visceral disease cutaneous tenderness is encountered, as well as vasomotor, secretory and other vegetative phenomena. In those cases where no parietal peritoneal involvement is demonstrable it is necessary to account for the area of skin tenderness. Cutaneous pain in definite areas was described by Hilton (7) in 1863 as of sympathetic origin. He stated that it was found "occurring on the surface of the body in association with derangements of internal and often remotely situated viscera." Lange (11) thought that all pain in visceral disease was purely reflex

in origin, and traced the impulses through afferent fibers of the vegetative nervous system to the spinal cord where radiation took place along the sensory tracts to the abdominal wall,—the location to which the mind projected the sensation. Although pain and tenderness may be strictly confined to the somatic spinal segmental area representing the involved viscus, that pain which occurs some distance away, and has no particular representation in this segmental area, is nevertheless a definite form of viscero-sensory reflex and is discussed under referred pain. Spiegel (24) adopts much the same viewpoint, and treats the subject of viscero-sensory reflexes in greater anatomical detail. He states that the impulses produced by the irritation of the peripheral terminations of the splanchnic nerves pass to the posterior horns, and are there diffused to the roots of the corresponding somatic nerves, so that the pain or tenderness seems to occur in the territory of the distributions of these nerves. Mackenzie is insistent in his opinion that the areas in the cord which are stimulated are irritable foci. Spiegel calls attention to the fact that in disease of the aorta the segmental skin area shows not only definite hyperesthesia, but also distinct vasomotor phenomena, which are either entirely obvious or can be brought out by slight pressure. In gastric ulcer and gall-bladder disease the pressure of a spatula over the hypersensitive area brings out dermographism and "goose flesh."

Ross's (22) viewpoint is that there may be either *true* visceral pain alone, or occurring in association with pain in the skin muscles and connective tissue connected with the same spinal segments. Hurst on the other hand calls attention to the frequency with which visceral disease is unaccompanied by somatic pain or tenderness. Ryle (23) believes that the occurrence of a viscero-sensory reflex means an inflammatory lesion of the viscus and states: "Visceral pain expresses a perturbation of visceral function (which may or may not be due to local organic disease), while the somatic phenomena generally express a structural lesion in the wall of the viscus."

VISCERO-MOTOR REFLEXES

The pathway for a viscero-motor reflex must be the same as that explained by Speigel (24) for viscero-sensory reflexes. The impulse is carried from the viscus mainly by afferent splanchnic fibers to the posterior root and posterior horn cells, and through synapses with anterior horn cells it stimulates, in the corresponding segment, the

skeletal muscles to contraction. A familiar example of a viscero-motor reflex is the rigidity of the muscles in the right lower quadrant of the abdomen in appendicitis. Mackenzie definitely subscribes to reflex activity the rigidity of muscles in visceral disease, and holds that the purpose of it is the guarding or protection of the underlying diseased organ.

Miller (16) has proved experimentally the existence of viscero-motor reflexes in decapitated animals, by stimulating the central ends of various visceral nerves, thereby causing strong contractions of the recti muscles. This investigator believes that the drawing up of the legs in visceral disease is a defense reflex which aims to diminish intra-abdominal pressure. He has carried out many experiments along these lines and has found evidence of a much more widespread reflex than that concerning the particular spinal segment which represented the visceral area involved. The stimulation of the central end of the celiac nerves caused a contraction not only of the rectus abdominis, but also of the anterior tibial and gastrocnemius muscles. These contractions were at first tonic, and then became clonic. Stimulation of the central ends of the superior mesenteric nerves caused contractions of the iliopsoas, gastrocnemii and anterior tibial muscles. The intensity of the stimulus in these experiments of Miller's must have paralleled the intensity of the stimuli occurring in actual inflammatory lesions, to have enabled it to produce somatic activity.

Ryle (23) is of the opinion that it is only in inflammatory tension of the viscus that a viscero-motor reflex can occur. Miller and Simpson (17) have stated that they believe abdominal rigidity exercises a protective function in guarding a viscus from overdistension or from opposing the effects of gravity. The author presumes they meant protection in the absence of definite disease when they used the name viscero-tonic reflex.

Several writers have tabulated the spinal segmental areas through which viscero-motor reflexes occur in the case of any particular organ. They are generally agreed that in stomach disease the muscles innervated by the sixth, seventh and eighth dorsal spinal segments, show contraction; in liver and gall-bladder disease and in disturbances in the small intestines, the ninth and tenth dorsal segments; in diseases of the colon the eleventh and twelfth dorsal segmental muscles are involved. It is generally observed that the viscero-motor and viscero-sensory reflexes occur in the same segmental areas, a theory

which certainly adds to the belief that only stimuli of certain intensities reach the spinal cord and are there diffused to the motor and sensory cells. Perhaps anatomical proof of such reflex pathways is lacking, but physiologically there is no doubt of their existence.

REFERRED PAIN

For purposes of description and in the interest of practical orientation, if possible, the writer has limited the use of the term, viscero-sensory reflex, to pain or tenderness occurring in a spinal segmental area which also subserves the functions of the viscera involved; and he has restricted the term, referred pain, to that which is manifested in the distribution of a spinal segmental or cerebral area other than the one representing the diseased viscus. Referred pain, however, no matter at what point it occurs, when due to visceral disease, is as much a viscero-sensory reflex as it is a reflex limited to one spinal segment. Many authors consider all painful disturbances in visceral disease as referred pain, and there is no general agreement regarding localizable pain and irradiation of pain. Spiegel (24) believes that irradiation commonly takes place through the posterior horns, and that patients definitely localize the pain in the irradiation area and not where it actually occurs.

Head (6) studied intensively the various cutaneous pain and tenderness areas, and attempted to chart these areas with the idea of associating them with disease in definite structures. Although his work was conscientiously done there has been no definite corroboration, by other investigators, of areas of cutaneous hyperalgesia occurring at points a great distance from the somatico-visceral spinal segmental areas. He expressed the opinion that the viscera are endowed with "deep and protopathic sensibility in a low degree," but that the chief pain in visceral disease is referred pain. Ross (22) does not support Head's views, stating his belief that referred pain is always confined to the skin, muscles and connective tissues related to the same spinal segment.

Pain in the back in esophageal disease is called referred pain by Hurst (6) and that felt beneath the sternum anteriorly, local pain. He believes the referred pains all radiate laterally, and that the greater the sympathetic nerve-supply to a viscus, the greater will be the cutaneous referred pain. The cutaneous tenderness is greater since

the spinal segment involved is under these conditions more irritable. The "brow-ache" that occurs when eating iced food is traced by Hurst through vagal afferent fibers to the medulla where the neighboring fifth nerve nucleus is stimulated, and the pain is referred to the peripheral distribution of the fifth facial nerve. Although other authors state that this brow-ache is due to the effects of the cold in contact with the nerves of the hard palate, there are occasional clinical instances of disease of the cardia showing pain in the face, which disappears on the clearing up of the esophageal disease. Bolton (2) points out the same relationship between tenth nerve involvement and fifth nerve manifestations.

Ross (22), Mackenzie (15), and Head (6), all subscribe to the viewpoint that in visceral disease a focus of irritation is set up in the spinal cord, and that sensory impulses from other parts, passing into this segment are so exaggerated as to be painful.

Bolton (2) states that the referred pain in the back in visceral disease is more extensive than the anterior pain and much more indefinite. He believes that pain commonly radiates from the front to the back and is limited to a particular cord-segment, but that irradiation takes place over a wide area,—involving several cord-segments. The irradiation occurs most frequently upwards from the segment originally involved but occasionally downwards, though confining itself definitely to cord-segments.

Spiegel (24) sums up his comments on Head's work by stating that the so-called "Head's zones" represent the effects of visceral innervation upon cutaneous sensibility, and that the pain may be located over the diseased organ; or some distance away (as in angina pectoris or renal colic) due to the embryologic separation of the cutaneous nerves; or, lastly, quite a distance away, due to irradiation.

Ryle (23) emphasized the point that research into the problem of referred pain and visceral pain is out of the hands of the experimentalist, because pain cannot be subjectively recognized in animals.

Head (6) finally concluded that the areas of cutaneous tenderness in visceral disease do not correspond to cortical or to peripheral nerve-distribution, but represent the supply of pain, thermal, and trophic fibers to the skin from various spinal segments, without particular correspondence to posterior root distribution. Bolton finds areas of cutaneous hyperesthesia to be of small value in diagnosis, as a general rule, because they are so uncertain and irregular in

occurrence. Although Head confines pain in the back in gastric disease to the seventh and ninth dorsal areas, Bolton states that he has found it extending from the eighth dorsal to the second lumbar nerve.

Head's explanation of referred pain is as follows: "When a painful stimulus is applied to a part of low sensibility in close central connection with a part of much greater sensibility the pain produced is felt in the part of higher sensibility rather than in the part of lower sensibility to which the stimulus was actually applied."

SUMMARY AND CONCLUSIONS

Sensation in the gastro-intestinal tract is produced by overcontraction or overdistension of the muscle-coats, and is, therefore, "muscle sensibility."

The only conscious sensations arising from the gastro-intestinal tract are pain and discomfort. The pathways by which these impulses are conveyed to the higher centres for interpretation are not anatomically proven, but there is sufficient physiological evidence to warrant the statement that definite central connections and pathways exist. The most probable routes by which pain-impulses reach the cerebrum are by way of afferent vegetative fibers through posterior roots, posterior horns, and the anterolateral tracts of the spinal cord.

Localized pain in a viscus is not satisfactorily proven, but clinical evidence supports the contention as to its existence.

Viscero-visceral reflexes in the gastro-intestinal tract may be divided into four groups:

1. Viscero-visceral. Disease in one organ may give no symptoms referable to it, but may manifest itself by some type of disturbance in a neighboring or in a distant organ.

2. Viscero-sensory. Through segmental viscero-somatic representation disease of any organ may be manifested by pain and tenderness in the corresponding skin area.

3. Viscero-motor. Through the same connections as mentioned in §2, there may be a segmental muscular response, i.e. rigidity.

4. Referred pain. This is in reality a viscero-sensory reflex, but may occur at a great distance from the organ involved. It cannot be accounted for satisfactorily in the majority of instances, on definite anatomical evidence, but in all probability the reflex occurs through the cerebrospinal pathways.

DISCUSSION

The following questions submitted to Dr. Patten before the Commission, together with the answers to them, are here reported verbatim.

Dr. Cannon: There was one remark made by Dr. Patten that I think might be commented upon.

He pointed out that peristaltic waves, and the processes of digestion, went on quite satisfactorily unassisted by the sympathetic division of the autonomic system. It is that division that *interrupts* all these processes. So that it is quite natural that the processes should go on without any disturbance with the sympathetic division removed.

I recall that many years ago, when I first saw all this beneficent process of digestion interrupted by signs of anxiety, or rage, or distress on the part of the animal, it seemed to me that the logical thing to do was to remove the sympathetic system in order to prevent disturbance of the digestive process, and it was only after further study of the influence of the emotions that this interruption of digestion took its place in the total picture. The digestive process, as I see it, is interrupted because blood is needed elsewhere in critical emergencies and the digestive process using blood, can be set aside temporarily, so that the total energies of the organism can be utilized for the struggle, whatever it may be, fight or flight, that may be required because of the exigencies of the moment.

All these phenomena which you have been observing are promptly stopped whenever excitement of a grave character or even of a minor character—even worry or anxiety—appears.

Dr. Cobb: Mr. Chairman, I should like to ask Dr. Patten about the actual technique of this film. He speaks of it as being rather normal. I should think that an animal under urethane, with the abdomen open and the illumination strong enough, might well have the irritation of abnormal heat.

I must admit that in the observation of those extraordinarily interesting "movies," I was rather lost. The picture looked to me like a squirming mass. I was unable to make out any real progression.

Then Dr. Patten mentioned the afferent vegetative nerve-fibers. I have always been rather confused as to the exact anatomy of these afferent vegetative nerve-fibers. How do they reach the spinal cord? I should like to know if there is any accurate knowledge on the anatomy of this.

Dr. Patten: In regard to the first question, Dr. Cobb, I know nothing about the conditions under which these pictures were taken. I happened to see them and was very much impressed because they gave a visual picture of what goes on. Perhaps it approaches the normal as nearly as anything we can get, under the abnormal circumstance of having the abdomen opened.

In regard to the second question, in all of my studies on the subject I confess that I have had the same impression as you: that there is no definite knowledge concerning the actual anatomical localization of some of these structures. It is

only through physiological activities that such pathways have been expressed, and in my paper I have purposely avoided taking up the question of the exact anatomical distribution because I think it is one which the physiologist can answer much better than I.

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CHAPTER XXIII

HEAT- AND COLD-SENSITIVENESS

Relationship to Heat-Prostration, Effort-Syndrome, Asthma, Urticaria, Dermatoses, Non-Infectious Coryza, and Infections

WILLIAM W. DUKE, M.D.

INTRODUCTION

IN THE following paper a series of relatively common illnesses are enumerated, many of them serious, which are caused, the author believes, by a disorder in the heat-regulating mechanism. These illnesses include heat-prostration, symptoms of effort-syndrome, non-infectious coryza, asthma, urticaria, dermatoses, and other miscellaneous ailments. They are commonly diagnosed as neurasthenia, psychasthenia, allergy, atopy, vagotonia, and eczema. The patients are hypersusceptible to infection during reaction, especially to infection in the naso-respiratory tract, and for this reason, their illness is often classified with the infections.

THE HEAT-REGULATING MECHANISM

The heat-regulating mechanism is one that is very important and very effective. It is important because it constitutes the difference between warm-blooded and cold-blooded animals. It is effective because it maintains body-temperature at a relatively constant level in the normal individual, whether he resides at the equator or in the polar regions, and whether he generates an enormous amount of heat through effort, or whether he is at rest or asleep.

Investigation of this heat-regulating mechanism has interested such eminent physiologists as Claude Bernard (12), Richet and his associates (1, 39, 40), Cannon and others (14, 15). Many facts of fundamental importance have been disclosed which should claim the attention of pathologists and physicians, especially of those whose work brings them into contact with the disorders commonly classified as allergy or atopy, and with the so-called neuroses and the dermatoses.

Body-temperature is kept normal and constant through the auto-

matic control of heat-generation and of heat-loss. This automatic control is considerably strengthened by the voluntary actions of the individual when he feels too hot or too cold. Whereas the automatic and voluntary control of heat-generation is exceedingly important, it is not so effective, under average conditions, as the automatic control of heat-loss. Both mechanisms, however, are important.

OVERHEATING

Heat-generation is augmented in a given organ by an increase in its activity, whether the organ be the brain, a gland, or a muscle. If the excess heat so generated is not immediately removed by an increased blood-flow, the organ is likely to become overheated and to behave badly. It may even become permanently damaged by overheating. The temperature at which an organ works to its best advantage is unfortunately so dangerously near a temperature which is damaging to its function that the prompt removal of heat from an active organ is of equal importance with the prompt removal of waste products. Hyperemia is looked upon as useful in its capacity for carrying additional food and oxygen to an organ during periods of activity, and for the removal of carbon-dioxide and other waste products.

The foregoing facts seem so apparent as scarcely to need discussion. However, it may be well to emphasize the gross importance of a slight excess of heat as a disturbing and dangerous element by quoting several interesting experiments. Moore and Oslund (35) state that the temperature of the scrotum is several degrees below the average temperature in the peritoneal cavity. By wrapping a ram's scrotum in such a way as to cause a rise in scrotal temperature toward the temperature of the peritoneal cavity, these investigators made the spermatozoa disappear from the testicle almost completely within a few months. They believed that this phenomenon was actually due to a rise in temperature above the optimum for this tissue, and that the cause of the absence of spermatozoa in undescended testicles lies primarily in the fact that the peritoneal temperature is above the optimum for the normal life of spermatozoa. Heymans (25) states that the brain of an animal is more sensitive to high temperature than are its other organs, and that a brain-temperature of 42° to 43°C. is fatal for rabbits. Heymans and Heymans (26) found that brain-temperature exceeding 45° to 46°C. in dogs causes the death of the brain-cells. Storm van Leeuwen and van der Made (30) found that

the reflexes in the cat are most active at a temperature of 38°C. and that they are rendered less active by a rise in temperature above this point. Lowering the temperature to 35°C. has little effect upon the reflexes, but below this point it reduces them. All observers seem to find that animals stand a lowering of temperature much better than a rise above the optimum.

The above statements refer to the overheating of individual organs. Activity of several organs gives rise to a general increase in body-temperature under normal conditions, unless heat-loss from the nose, bronchial tubes or skin can be adequately increased. Heat-loss can be increased through the dilatation of the vessels leading to the three important cooling surfaces, the skin, the mucous membrane of the bronchial tree and of the nose. Cooling is aided by the secretion of moisture and the evaporation from these surfaces, and by an increase in the depth and rapidity of respiration. If the air is dry, evaporation is an important factor in the process of cooling. If the air is saturated with moisture, the surfaces are cooled entirely by convection and conduction to the outside air. If the outside air is moist, but cool, it may adequately cool the body. If, however, the outside air is moist and warm, heat-loss is very seriously retarded and under these conditions, it is extremely easy for activity to cause overheating, illness and death.

Cerebral Heat-Control

Automatic control of body-temperature is accomplished through the co-ordinated action of many structures which try to govern heat-production and heat-loss. Body-temperature is regulated partly by a thermostat-like mechanism in the region of the thalamus. Barbour (3 7), Moore (36), Hashimoto (24), and others have demonstrated that by cooling an area in the region of the corpus striatum, rectal temperature can be increased, whereas by warming the same area, rectal temperature can be reduced. Isenschmid and Krehl (27) have demonstrated that the power to resist external temperature-changes without variation in body-temperature, is lost in animals if the mid-brain is sectioned just anterior to the centre of the optic thalamus. Experimental injury to the optic thalamus in pigeons causes them to lose their power to resist changes in external temperature (Rogers (41, 42)). Resection of the stellate ganglion has the same effect (Freund (21–23)). Such experiments harmonize well with clinical

knowledge. Brain disease caused by hemorrhage, tumor, meningitis or trauma is likely to be associated with rapid oscillations in body-temperature. There should, therefore, exist little doubt concerning the existence of the automatic control of temperature by the brain centres.

Endocrine Heat-Control

Several of the glands of internal secretion, especially the adrenal, thyroid, and pituitary, play rôles in temperature-control. The effect of hyper- and hypothyroidism upon the metabolic rate is so well known as to need no discussion. When the metabolic rate is abnormal in a dysthyroid case, the altered rate of heat-production is often compensated for by an altered rate of heat-loss so that the body-temperature is not correspondingly altered. The adrenal gland has an effect both upon the rate of heat-production and heat-loss, the former through modifying the metabolic rate, the latter through an effect upon vascular tone and therefore upon blood-flow to cooling surfaces. Boothby and Sandiford (13) review the literature on the subject of the adrenal gland in relationship to heat-production, and confirm the results of other observers in showing that the injection of adrenalin into animals even in physiologic doses, noticeably increases the rate of heat-production. Aub, Forman, and Bright (2) find that removal of the adrenal glands is followed by a drop of about 25 per cent in the metabolic rate, even though the body-temperature remains the same. McIver and Bright (33) find that the direct or reflex stimulation of adrenal secretion promptly aguments metabolism, often as much as 50 per cent. Cannon, Querido, Britton, and Bright (15), find evidence of an effect of adrenal secretion on the heart-rate in animals exposed to a cold environment, or upon the introduction of cold water into the stomach. This cold-reaction could be stopped by the application of heat. In animals in which one of the adrenal glands was denervated, and the other removed, the heart-rate was not affected by cold. Furthermore, an increase in the metabolic rate in normal individuals was demonstrated after the introduction of cold water into the stomach through a tube. If cold applications were great enough to cause shivering, the rise in metabolic rate frequently amounted to as much as 50 to 90 per cent above the basal. These investigators concluded that the same conditions increase the adrenal secretion in animals and the metabolic rate in man, and that "a disturbing heat-loss evokes

activity of the adrenal medulla and that the output of adrenin by hastening combustion serves to protect the organism against cold." They supported the contentions of von Voit (49, 50) and Rubner (43, 44) that there exists in the body a mechanism for the chemical augmentation of metabolism. They believe the secretion of the adrenal gland is augmented by cold and that this serves to increase the rate of heat-production. Adrenal secretion is believed to be governed both by the temperature of the blood and by sensory impulses coming from the skin and other areas and caused by heat or cold.

The pituitary hormones have a profound influence on growth and metabolism, but apparently little effect on heat-production. This point has been intensively studied both clinically and experimentally, but only negative or variable results have been obtained. Both adrenal hormones and pituitary hormones, however, are interesting in relationship to heat-loss since the hormones of either gland have a profound influence upon vascular tone. The intracutaneous injection of an extract of the adrenal or of the pituitary gland in dilute solution causes vaso- and capillary constriction, with blanching of the tissues. There is some uncertainty as to whether or not there is an adequate quantity of adrenalin in normal blood to effect vascular tone. Krogh (28, 29) is inclined to believe that the pituitary hormone is more important than adrenalin in this rôle—that is, as a normal regulator of capillary tone. Rehberg and Carrier (38) found that extirpation of the pituitary gland caused loss of capillary tone in frogs, and Pohle (37) found that its extirpation can lead to actual edema.

Histamine Effects

The intracutaneous injection of a dilute solution of histamine causes local hyperemia, itching, and edema—in fact, a typical hive (Eustis (20)). Lewis (30, 31) has recently emphasized the importance of histamine and allied bodies (which he calls H-bodies) in relationship to vascular tone under physiologic conditions. His work is based upon a study of the skin vessels, but he infers that the same influence may be exerted upon the vessels in other areas as, for example, upon those supplying muscle-tissues. Histamine-like bodies are interesting because they are liberated by putrefaction from protein foods, and also because they can be isolated from normal tissues by normal catabolic processes. Upon injection, histamine has an opposite effect

to that of pituitary extract or of adrenalin in that it causes capillary dilatation almost immediately. Lewis (31, 32) finds that the effect of histamine upon capillary tone is more profound than that of either pituitary or adrenal extract; because vessels which are dilated with histamine cannot be contracted with either pituitary or adrenal extract even when used in relatively concentrated solution.

Pituitary hormone, adrenal hormone, and histamine-like bodies, therefore, working antagonistically and causing respectively vasoconstriction and vasodilatation, must be looked upon as possible important factors in the regulation of the blood-supply and, therefore, important factors in the regulation of heat-loss. Inasmuch as histamine-like bodies are liberated by normal metabolic processes, their influence in causing vasodilatation and increased heat-removal cannot be overlooked as probable important factors in the regulation of the temperature both of the active organs and of the body as a whole. This phase of the subject will be referred to subsequently in a clinical discussion.

Sensory Heat-Control

Whereas in the previous paragraphs emphasis has been laid upon hidden mechanisms which effect heat-production and heat-loss, the author does not wish to imply that the more obvious factors are less important. For example, the sense-organs for the perception of heat and cold have, no doubt, a rapid effect upon heat-generation and heat-loss, both automatic and voluntary. Richet (39, 40) believes that reflexes from sensory nerves may cause the initial response to temperature-change. He noticed polypnea immediately after the exposure of dogs to sunlight, even at a time when rectal temperature was temporarily falling. The fact is, that the application of heat to the skin in doses which could hardly cause any marked change in blood-temperature, may cause a quick change in the metabolic rate. Furthermore, the immediate effect of exercise upon the respiratory rate is so obvious and great as not to need experimental proof. It would be interesting to note whether or not there is a reduction in the tone of the muscles of the bronchioles and pulmonary vessels coincident with exercise, which would aid in body-cooling. This, one would think, should exist but so far as the author knows, it has not been experimentally proven.

SURFACE TEMPERATURE IN RELATIONSHIP TO RECTAL TEMPERATURE

Contrary to general belief, temperature is not the same in different parts of the body, nor is it constant in all localities under varying conditions of external temperature. For example, the temperature of the skin and of the tissues immediately beneath the skin, is greatly below rectal temperature. Average skin-temperature, depending upon the body-covering, may vary from 24° to 34°C. and may become lower after exposure to cold. The skin-temperature and muscle-temperature of the extremities are, as a rule, much less than rectal temperature, and upon exposure to cold, are reduced rapidly and to a surprising degree. Skin-temperature, under the influence of exercise, has been studied by Benedict and Parmenter (11), who find that average skin-temperature is not increased, but is actually reduced one or more degrees, by physical exercise in cold air, even though the metabolic rate may be increased as much as 500 per cent.

Under basal conditions about 75 per cent of body-heat is lost by radiation from the skin. In periods of activity, however, a large proportion of the excess heat is lost, not by radiation, but by evaporation and convection from the respiratory tract. Apparently, during exercise, constriction of surface vessels forces blood into internal channels where it supplies active tissues. The excess heat collected there, is discharged through the pulmonary circulation into the respiratory tract. The latter is a great factor in heat-removal in animals which do not sweat.

THEORY OF TEMPERATURE-CONTROL

Richet's theory of the normal control of body-temperature assumes that reflexes caused by the sensation of heat or cold on surface tissues, give rise to prompt reactions which control body-temperature under the usual conditions of living –that is, they modify heat-production and heat-loss so that body-temperature remains the same. He believes that mechanisms which are affected by the temperature of the blood itself, are less important and play important parts only after considerable change in blood-temperature has occurred.

Bazett (8–10) combines the views of Richet (39, 40), the dual heat-centre theory of Meyer (34), and the experimental work of Sherrington (45–46), and suggests the following hypothesis: The control of body-temperature is almost entirely reflex, caused by sensory impulses from surfaces, which are due to heat or cold. He believes that

changes in blood-temperature are effective chiefly by giving rise to a condition in the central nervous system which causes exaggerated responses to sensations of heat or cold. He assumes, for example, that a fall in the temperature in the central nervous system gives exaggerated responses to the sense of cold, thereby causing a warming of the body; whereas, a rise of temperature in the same area, gives exaggerated responses to the sense of warmth, leading to a general cooling of the body. In other words, the optimum brain-temperature for reflexes giving rise to cooling and warming effects, are not identical.

It is impossible in an article of the present scope to do justice to the literature and investigations in this field. The author can only emphasize that an abnormal rise in temperature in a given organ is damaging to the health and functional activity of the organ; that an abnormal rise in body-temperature, in general, is damaging to the health and activity of the individual; and that there is a remarkably effective and very complex mechanism which provides, under normal conditions, for the adequate cooling, both of the individual organs and of the body as a whole. Defective regulation of heat may induce abnormal responses in any of the three important cooling surfaces—the skin, the nasal mucous membranes, the bronchi—and cause serious pathological conditions in these localities.

FEVER

When heat-production exceeds the elimination-rate, the temperature rises and fever occurs. Fever, as observed in the infectious diseases, is not always attributable to increased heat-production. It is caused quite often by reduced heat-loss. This fact is evident, since the increase in metabolic rate observed in malaria and typhoid fever, is not as great as that caused by exercise or over-eating. Furthermore, in some of the infectious diseases associated with fever, the metabolic rate is actually reduced.

It is stated in many of the text-books on the practice of medicine and therapeutics, and probably correctly so, that in febrile conditions the heat-regulating mechanism is working at an abnormally high level. Consequently, responses to a normal body-temperature simulate those normally caused by a reduced temperature and give rise to a retention of heat. In harmony with this view, it is found that the skin of patients with fever is frequently hyperesthetic to cold. In the same way, the subnormal temperature so frequently observed

during convalescence from febrile diseases, might be accounted for by assuming that the heat-regulating mechanism is then working at an abnormally low level, so that normal temperature under these conditions would give rise to the responses normally caused by heat.

ACCLIMATIZATION AND DECLIMATIZATION

Healthy persons tolerate conditions which vary tremendously in air-temperature and air-moisture. For a sick individual, however, a rapid change from one extreme to another, may result seriously. Through gradual change, the same individual may become so acclimated as to tolerate the new conditions without ill-effect. Races become so acclimated to extreme conditions that they live in comfort in atmospheres which prove injurious to newcomers. Individuals visiting the tropics, sweat much more than natives. Evidence of acclimatization was noticed by Vernon (47, 48), in experiments on muscular work in warm rooms. Bazett (8–10) noticed acclimatization, after ten or twelve exposures, in students kept in warm, moist chambers for periods of one hour. Individuals living in temperate zones feel the effect of the first hot days of spring and early summer more than they do the hotter days of later summer. Likewise, they notice the effect of the first cold days of winter more than they do the colder days later in the season. Finally, individuals who have been exposed for an hour or more to cold, notice the effect of heat more than if they have not been so exposed. And the reverse is also true.

The effects noted in normal individuals are far more pronounced in patients. For example, those with asthma or pruritus are unfitted for the cold days of winter, by the prolonged summer heat. They may gain tolerance for cold during the winter months. Others may be unfitted for the heat of summer by prolonged exposure to cold during the winter months. In individuals of this sort, seasonal weather changes may have serious ill-effects which are not noticed in normal individuals.

MANIFESTATIONS OF HEAT- AND COLD-SENSITIVENESS

Certain individuals, for one or several causes, become abnormally sensitive to the effects of heat or cold. The abnormal responses of such persons may be classified as follows: (*a*) general or constitutional reactions; (*b*) reactions referable to one of the three cooling surfaces—the skin, the nasal mucous membrane, the bronchi; (*c*) reactions referable to an internal organ.

Reactions of sensitiveness to heat or cold vary in intensity, in the speed with which they appear, and in location. In some patients, the reactions seem to be chiefly constitutional. Examples of this type are cases of heat-prostration and effort-syndrome. In others, reactions may be referable chiefly to one of the cooling surfaces. Classical examples of this are thermic coryza, thermic asthma, and thermic urticaria, or eczema. In others reactions may be referable chiefly to an organ. An instance of this would be thermic headache or gastric disturbance caused by temperature-change or by effort.

Constitutional Manifestations of Heat-Sensitiveness; Their Relationship to Heat-Prostration, Effort-Syndrome and Syncope

Lewis's "effort-syndrome" is frequently caused by sensitiveness to heat (31, 32). Patients of this type, after effort or exposure to hot moist air, often give a history of exhaustion, weakness, dizziness, tremor, fainting spells, or a tendency to faint, a feeling of oppression in the chest, palpitation, anorexia, nausea, or vomiting. One or all of these manifestations may appear consistently as an effect of effort or of overheating. Heat-sensitive patients of this kind are exhausted by effort, especially on hot, humid days. Heat, mental effort, or physical effort may each have the same effect in highly sensitive cases. The reaction may be so marked that the patients may be unable to tolerate the mental effort of watching athletic contests or of attending to an interesting business deal. Likewise, they may be unable to tolerate the physical effort of climbing up on an examining table quickly. Finally, they may be unable to tolerate as much heat as is encountered in the drinking of a cup of hot coffee or in the placing of their arms in a water bath of 42°C. for thirty seconds. In a specific instance, a patient lost consciousness during a mild heat-test but was revived immediately by an ice-rub on the arms.

The author feels that many cases of heat-prostration and syncope are due to heat-sensitiveness. Patients who are highly sensitive to heat instinctively avoid heat and avoid effort on humid, hot days. If they are so unfortunate as to be unduly exposed to heat or are forced to make an effort in hot, humid weather, they may faint and in case the exposure is great enough, may be actually shocked.

The identity of the above condition and Lewis's effort-syndrome would seem apparent. Lewis mentioned in his classical description of the effort-syndrome that symptoms are often brought to the surface

through a change in habit, such as that produced by the drafting and drilling of men who had instinctively sought out sedentary lives. The author has found examples of effort-syndrome in individuals who give a history of exhaustion, weakness, dizziness, breathlessness, and tremor after effort and who show precisely the same symptoms while absolutely quiet if they are heated by a hot lamp, or a diathermic current, or if they immerse their hands and fore-arms in a water bath of 42°C. Likewise, their complaint can be immediately relieved by the cooling effect of an ice-rub on the arms and chest. Furthermore, these patients can usually tolerate a moderate grade of effort if they are simultaneously cooled.

Lewis (31, 32) made the important observation in his study of the effort-syndrome that in a large proportion of cases the symptoms followed an acute infectious disease. This, likewise, is true in the author's series of heat-sensitive cases. A large proportion of the patients who show no definite physical defect, can definitely date the time of onset of their symptoms to a febrile disease.

A curious phenomenon can very frequently be demonstrated in this type of sensitiveness. Symptoms can be elicited not only by immersing the hands and fore-arms in a water bath at 42°C., but can be induced even if tourniquets are applied around the arms above the elbow so tightly that blood can neither enter nor return from the arm. Strange to relate, symptoms brought out in this way can be caused to disappear almost immediately if the fore-arms are rubbed with ice, even if the tourniquets have not been removed. Removal of the tourniquets before the application of ice does not materially add to the severity of the complaint or to its relief. This observation has caused the author to believe that symptoms in heat-sensitive cases of this type are in part a response to a sensation of heat and that the application of ice to the skin is an effective remedy even though it cannot directly lower body-temperature. In one case of urticaria so highly sensitive to heat that the immersing of one hand in a water bath at 42°C., would cause generalized erythema, pruritus, and urticaria, the immersing of one hand in warm water and the other in cold would have no ill-effect,—that is, the effect of heat in one case could be neutralized immediately by cold in another area. Furthermore, the effect of heat produced by effort could also be prevented or immediately stopped by the effect of cold on the skin.

Symptoms Similar to Effort-Syndrome Caused by Cold and Relieved by Heat

The manifestations of cold-sensitiveness may be identical with those of heat-sensitiveness discussed above, except that the symptoms may be brought out by cold instead of by heat or effort. Patients of this sort are inclined to seek out lives of activity and if active enough, they are inclined to feel healthy. Exposure to cold, however, especially when the patient is quiet, may cause symptoms such as exhaustion, weakness, dizziness, tremor, palpitation, oppression in the chest and nausea; in addition, such exposure may cause symptoms referable to one of the cooling surfaces that is, the swelling of the mucous membrane of the nose, bronchial tubes, or skin. Exposure may also give rise to symptoms referable to disorder in one of the internal organs, such as headache or precardial pain.

In individuals sensitive to heat or cold symptoms can often be reproduced objectively by rubbing the skin with ice or by having the patients immerse their fore-arms and hands in a water bath at 15°C. In the latter case, symptoms very often can be brought out even if tourniquets are tightly applied around both arms above the elbow. The release of the tourniquets may add little or nothing to their symptoms. Immersing the arms in warm water or the application of heat to the chest may give relief within a very short time. These symptoms like those of heat-sensitiveness seem to occur as a response to the sensation of cold and can often be neutralized by creating the sensation of heat in another locality.

Symptoms Referable to the Cooling Surfaces—i.e., the Nasal Mucous Membrane, the Bronchial Mucous Membrane and the Skin

This class of disorders is very important and very great, and may appear in heat-sensitive cases under the influence of increased heat-production or of reduced heat-loss; or in cold-sensitive cases under the influence of reduced heat-production or increased heat-loss. They may also appear apparently as a result of a sensation of heat or cold. They can be brought out objectively in the same way that the constitutional symptoms just described can be induced—that is, by heat or effort in heat-sensitive cases, and by cold and inactivity in cold-sensitive cases.

The nasal symptoms consist of sneezing, swelling of the membranes of the nose, with the increased secretion of clear mucus. If the con-

dition is perennial and of years standing, chronic edema of the membranes may lead to infection or polyps or to both. If the swelling is marked, it frequently causes headache.

The bronchial symptoms consist of a feeling of oppression in the chest, cough, and in the more marked cases, bronchial obstruction giving rise to asthma. This condition is very frequently accompanied with expectoration of clear mucus, and where the condition is chronic, infection may be superimposed, giving rise to true bronchitis.

The skin symptoms may consist of erythema, itching, urticaria, angioneurotic edema, and if the condition is chronic, of one or more of the following abnormalities; desquamation, increased secretion from the skin, thickening of the epidermis, cracking of the skin and occasionally of herpetiform eruptions. In chronic cases, especially in those which have prolonged, delayed reactions, the dermatoses may assume grave and ugly proportions. Swelling, redness, desquamation, secretion, and cracking can render the patient unsightly and most miserable. Infection may be superimposed, giving rise to multiple suppurations. There is one class of cases which have skin as dry as parchment. They never sweat nor can moisture be felt on the skin. One case, observed by the author, had a dry, parchment-like rash resembling ichthyosis, which was made worse by heat or by effort. This class of cases may be the same as those described in the literature which show wide oscillations in body-temperature in patients who do not sweat. The dermatoses caused by heat- or cold-sensitiveness may be generalized, may occur in patches, or may be confined to the exposed parts. The conditions are diagnosed under a wide variety of terms.

Symptoms Referable to an Internal Organ

These symptoms are almost too numerous to mention. They frequently appear as a result of the effect of heat or cold or of effort. They may occur in some individuals who seem physically normal, and in others, in whom a pathological condition can be found. In the latter, symptoms may be caused by strain. It accounts for the rapid exhaustion of individual organs observed so frequently in older people suffering from arteriosclerosis. As characteristic examples of this may be mentioned, profound mental exhaustion under the influence of excitement, emotional disturbances, or mental effort; precardial pain and palpitation under the influence of a little effort; abdominal

pain, following a little effort; and pain in the joints or in the muscles, following effort. In cold-sensitive cases, the identical symptoms may be caused by cold and by prolonged inactivity. These symptoms can often be reproduced under observation by the adequate application of heat or cold and can be relieved by the reverse application.

Combined Sensitiveness to Heat and Cold

The situation is further complicated by the fact that many patients react to body-heat most markedly if simultaneously exposed to surface cold. Likewise, other types react to body-cold most markedly when exposed to surface warmth, that is, to warm, humid air.

For example, certain asthmatic patients, sensitive to heat and to effort, have reactions only when breathing cold air. They tolerate heat or effort better during the summer months than during the winter months. They tolerate effort better when indoors than when out-of-doors breathing cold air. This type of case may have asthma if he sleeps in a cold room and uses an excess of covering. He may remain free from reaction if he sleeps in a warm room and uses little covering. This advice has sufficed to relieve several severe cases of chronic asthma. Likewise cold-sensitive cases may tolerate body-cold if they are breathing cold air, but may have asthma or a nasal reaction if they breath warm, moist air. Cases of this sort are inclined to have attacks following cold baths in the summer. They may tolerate cold baths during the winter months. The cooling of the body by air-currents may precipitate attacks if the patient is breathing air which is warm and moist. The patient may tolerate air-currents easily if he is breathing air which is cool and dry.

The above reactions can be reproduced objectively by the appropriate application of heat, cold and effort, and can be relieved by a reverse application.

RELATIONSHIP OF HEAT- AND COLD-SENSITIVENESS TO INFECTION

In the early part of this work, the author learned that in testing patients sensitive to heat and cold, on several occasions he caused them to have febrile attacks which were diagnosed as bronchitis or coryza, and in two cases, pneumonia. In case of reaction, therefore, it is important to reverse the application immediately. Since this procedure has been followed, there have been no ill-effects from the tests.

Such experiences prove that patients, sensitive to heat and cold, are more susceptible to infections than are normal individuals, upon exposure to changes in temperature, and are prone to have one or several febrile attacks each year, usually with the changeable weather in the spring or fall. The situation is emphasized in the expression, "catching cold." Normal individuals can stand considerable exposure without "catching cold." Heat- or cold-sensitive cases can often stand very little.

RELATIONSHIP OF HEAT- AND COLD-SENSITIVENESS TO ATOPY

The relationship of heat- and cold-sensitiveness to atopy is interesting. Both conditions may have the same effect in causing so-called allergic coryza, asthma, dermatoses, and allergic shock. When an individual is specifically hypersensitive to an agent such as pollen or egg, and is also heat- or cold-sensitive, his symptoms are naturally aggravated greatly if he reacts to the material agent and to heat and cold at the same time.

Reaction to foreign agents, such as pollen or egg, has an unstabilizing effect upon the heat-regulating mechanism. The author has found it necessary, for example, to be more careful in making pollen injections in the treatment of hay fever and asthma on hot, humid days than when the weather is mild. A pollen reaction is frequently brought to the surface by exercise and heat after the patient leaves the office in good condition. An ice-rub applied to the chest and arms is an effective remedy for this type of reaction. Indeed, this ranks in its therapeutic effect second only to adrenalin.

The fact that thermal sensitiveness and pollen sensitiveness may occur in the same individual and that one of these conditions adds to the ill-effect of the other, might lead some to believe that the two conditions are identical. While both these types of sensitiveness may occur in the same individual, this is apparently the exception rather than the rule. Whereas pollen reactions and thermal reactions may occur simultaneously in an individual, they more frequently occur at different times of the year. Patients may have pollen hay fever or asthma during the fall months and may have identical symptoms caused by thermal sensitiveness during the winter months when the air is free from pollen.

RELATIONSHIP OF HEAT- AND COLD-SENSITIVENESS TO REACTIONS TO HISTAMINE-LIKE BODIES

Since the early writings of Eustis (20) upon histamine in relationship to the etiology of asthma and urticaria, writers have been attracted by the idea that histamine, if absorbed from the intestinal tract, causes the clinical manifestations of asthma and allied conditions. Since histamine-like bodies may cause symptoms similar to those produced by egg in egg-sensitive individuals, or by heat or cold in thermal sensitive individuals, the deduction that egg and heat or cold in certain persons, act through the liberation of histamine, would be an interesting idea. This could hardly seem a factor, however, in the patients previously mentioned who were caused to react to heat or cold applications on the fore-arms while tourniquets above the elbow prevented a return of blood from the arm.

PATHOGENESIS OF HEAT- AND COLD-SENSITIVENESS

Primary Cases

A large proportion of patients date the onset of their trouble from an acute febrile disease such as pneumonia, typhoid fever, tonsillar abscess, rheumatic fever, or one of the diseases of childhood. This is particularly true of younger individuals and in these, frequently no definite lesion of any sort can be found on most careful physical examination to account for their disorder except the history of a febrile disease (16–19).

Secondary Cases

In a minority of the younger individuals, and in many of the older patients, organic lesions are encountered which theoretically might disturb the normal heat-regulating mechanism; for example, organic disease in the nervous system, endocrinal disorders, arterial disease, or anemia.

The following are factors in the activity of the heat-regulating mechanism:

1. The sense-organs and afferent nerves which convey the sense of heat or cold to the higher centres.
2. The centres in the brain or spinal cord or elsewhere, which act as thermostatic regulators of temperature.
3. The complicated nerve-mechanisms: (a) which carry efferent

impulses from the nerve-centres controlling the caliber of the vessels supplying the active organs and cooling surfaces; (b) which modify the depth and rapidity of respiration; (c) which control the secretion of moisture on the cooling surfaces; (d) which carry impulses affecting the metabolic rate or causing shivering; and finally (e) which might cause one voluntarily to be more active or more quiet and to seek increased or reduced heat-loss.

4. The end-organs, such as vessels, active tissues, surface tissues, and secreting structures, which take part in heat-regulating.

5. The glands of internal secretion which furnish the substances directly affecting metabolic rate and also directly affecting the caliber of the vessels.

6. The presence of abnormal amounts of histamine-like bodies which can have an effect similar to pollen in pollen-sensitive cases, or to egg in egg-sensitive cases, and can cause reactions similar to those produced by heat or cold.

7. Finally, debilitating diseases, such as anemia, cardiac or renal disease, postfebrile conditions or senility, which weaken the organism as a whole and in this way indirectly interfere with normal responses to heat or cold.

The foregoing series is broad in scope. The heat-regulating mechanism is exceedingly complex and depends upon the co-ordinated action of many widely separated structures. A breakdown at any point may alter its normal behavior and cause trouble. The author believes the clinical symptoms in the skin, nasal, and bronchial membranes and perhaps elsewhere, are more often due to a spasmodic and defective response to temperature-change than they are to a direct effect of temperature-change *per se* on the tissues. They are analogous in this respect to the pathogenesis of a condition such as cirrhosis of the liver where defective efforts at repair do more harm than the primary injury.

HEAT-SENSITIVENESS PRODUCED EXPERIMENTALLY

The author has been able to render tadpoles and minnows sensitive to heat by injuring them with X-ray. In two series of experiments, each repeated a number of times, a little in excess of an erythema-dose of X-ray was administered to groups of tadpoles and to groups of minnows in shallow dishes of water. After a period of about two weeks, they were tested by placing them in beakers of water and

gradually raising the temperature of the water until they were killed. Both tadpoles and minnows treated by X-ray, showed little difference in activity as compared with normal controls tested similarly by a rise in temperature until approximately 35°C. was reached. Above this level, or thereabouts, each degree of rise had a more pronounced effect upon those subjected to X-ray than upon the untreated controls. The treated tadpoles and minnows, almost without exception, showed disturbed movements or began swimming on their backs or died at a temperature from one to three degrees lower than that which affected the controls. Both treated and untreated animals were handled identically and at the same time. Reducing the temperature to nearly the freezing point showed little or no difference in the behavior of treated and untreated specimens.

It was concluded that the X-ray so injures young tadpoles and minnows that they cannot adjust themselves so well to a rise in temperature above 35°C. as can normal untreated controls.

These experiments give a poor imitation of heat-sensitiveness as observed clinically. In the experiments, heat *per se* apparently does the damage. In the clinical cases, however, reaction to heat apparently does the harm. The rise of temperature *per se* is too trivial to account for the profound results which follow heat or effort.

CLINICAL EVIDENCE OF DISORDER IN THE HEAT-REGULATING MECHANISM

Evidence of disorder in the heat-regulating mechanism may be summarized as follows:

1. The Unstable Temperature

The patients almost always have a very unstable temperature. Instead of varying as it does in the average normal person around 98.6°F., with morning temperature slightly below the evening temperature, and with relatively slight change under the influence of average effort or exposure to heat or cold, the temperature is usually subnormal, is frequently almost constantly subnormal, and varies greatly in a majority of patients under the effect of altered heat-production or altered heat-loss. In the average mild case, the temperature runs between 96.4° and 98°F. The temperature almost never reaches normal, and frequently the morning temperature falls as low as 96°, or even 95°F. In one extreme case of heat-sensitiveness, the morning temperature was occasionally found as low as 92°F.

In these patients a change in temperature of one or two degrees up or down can often be caused by surprisingly small amounts of effort or by the application of heat or cold to the skin. If the temperature is abnormally low, a hot bath, the application of a hot lamp, or the immersion of the fore-arms in water at 42°C., will frequently cause a rise in temperature of from one to two or more degrees. Conversely, rubbing the chest or arms with ice or immersing the fore-arms in a water bath at 15°C. for from one to five minutes may cause a drop or occasionally a rise in temperature of one or several degrees. The above observations have been made a great many times on more than one hundred heat- or cold-sensitive patients, and are remarkably constant. Whereas a subnormal temperature is the rule in heat- and cold-sensitive cases, some of the latter (cold-sensitive cases) run a normal or slightly elevated temperature which is less variable than that found in the heat-sensitive cases. In the heat-sensitive cases, a subnormal, variable and unstable temperature-curve is almost constant except at odd intervals when patients have febrile attacks. During such attacks, they may be very ill, although quite often relieved of their sensitiveness to heat. Very frequently agents which stabilize the temperature and keep it up, give marked clinical relief to the patient. (See Figs. 112–118.)

2. Basal Metabolism

The basal metabolism is not so easy to study as body-temperature, and in the majority of cases the author was unable to demonstrate consistent changes which were definitely outside of normal variation. However, in a few cases, a high grade of abnormality and instability in metabolism was demonstrated. In several instances, the metabolic rate was as unstable as the temperature. It was found as low as from −40 to −58, on several consecutive days, in a patient who seemed physically perfect except for attacks of itching and urticaria which could be induced by effort or by heat. (See Figs. 119, 120.) In one patient, metabolism could be brought up to a normal rate within a few minutes through the effect of a little effort or by the application of a little heat to the skin. It may be said in passing that the outbreaks of hives in this case were believed to be the automatic erratic effort to compensate for the lowered metabolic rate and temperature change. When the rate was brought to normal the patient was clinically relieved of urticaria.

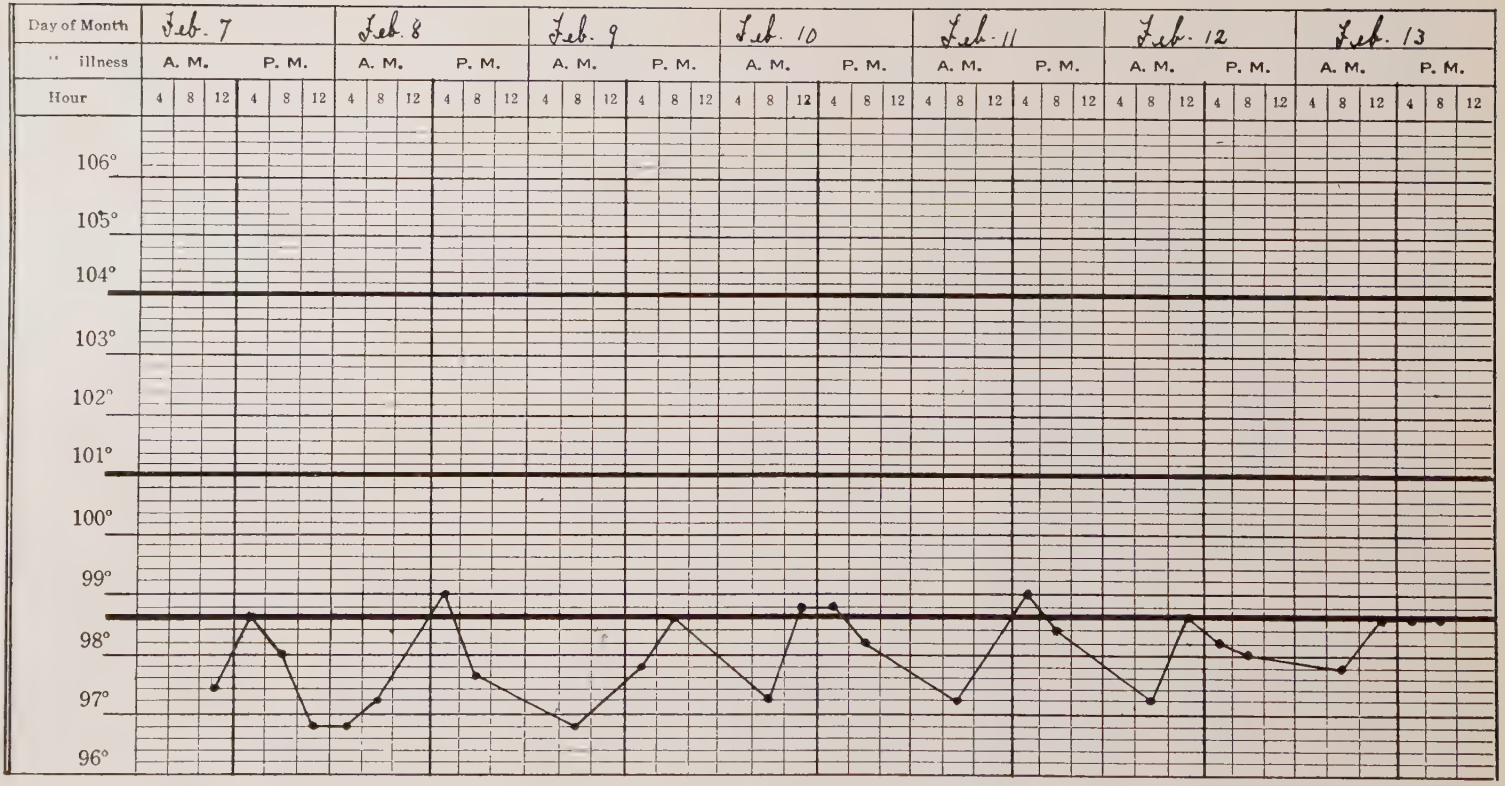

FIG. 112. Case of winter urticaria caused by sensitiveness to heat, especially after exposure to cold. Note the typical temperature-chart running almost constantly subnormal. When the temperature was raised to normal, or a little above, by the repeated use of typhoid vaccine, the patient was clinically very much better. His sensitiveness to heat, with its manifestations of urticaria, returned after the temperature again fell to its earlier subnormal levels. The basal metabolism was about normal.

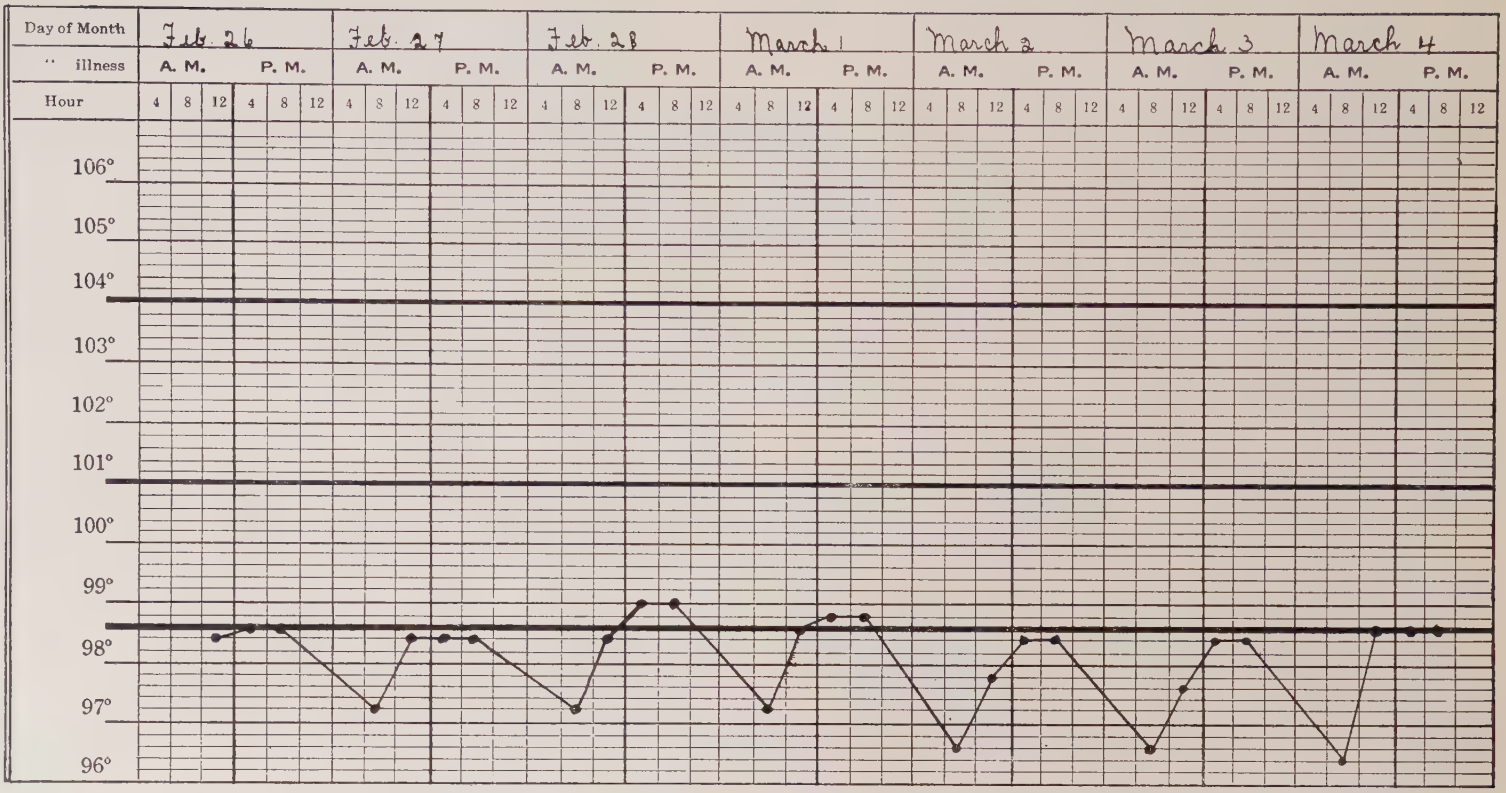

FIG. 113. A typical case of effort-syndrome and summer urticaria. Note that the temperature was almost constantly subnormal. In periods such as this, the patient would respond to heating with a nitrogen lamp, or to heating the fore-arms and hands with water at 42°C., or to a little exertion, mental or physical, with prostration or an outbreak of urticaria, or with both these effects.

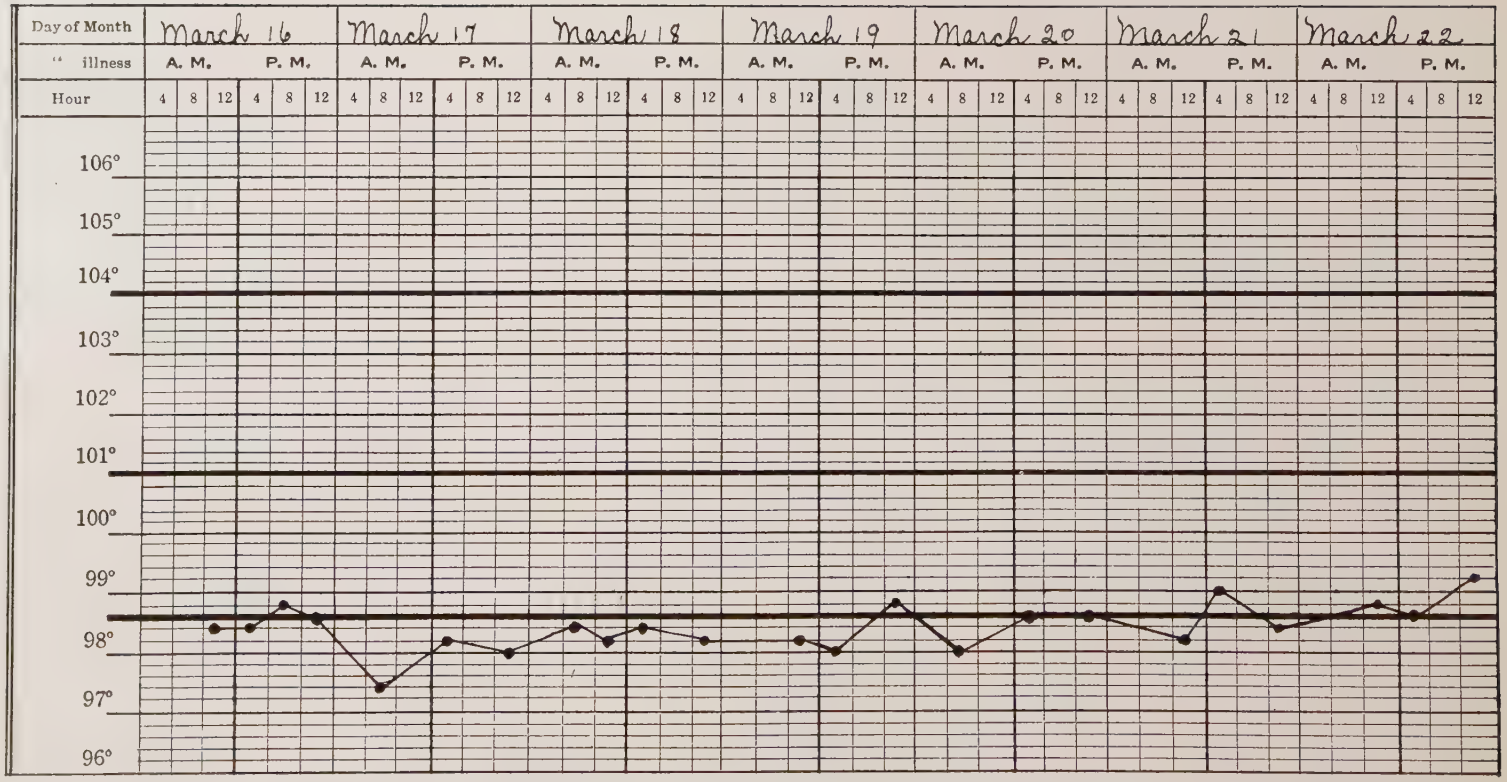

FIG. 114. Case of effort-syndrome and summer urticaria, shown in Fig. 113. Note the periods of a more normal temperature-level. At such times the patient could tolerate the degrees of heat that she encountered in her usual activities. The basal metabolism was about normal.

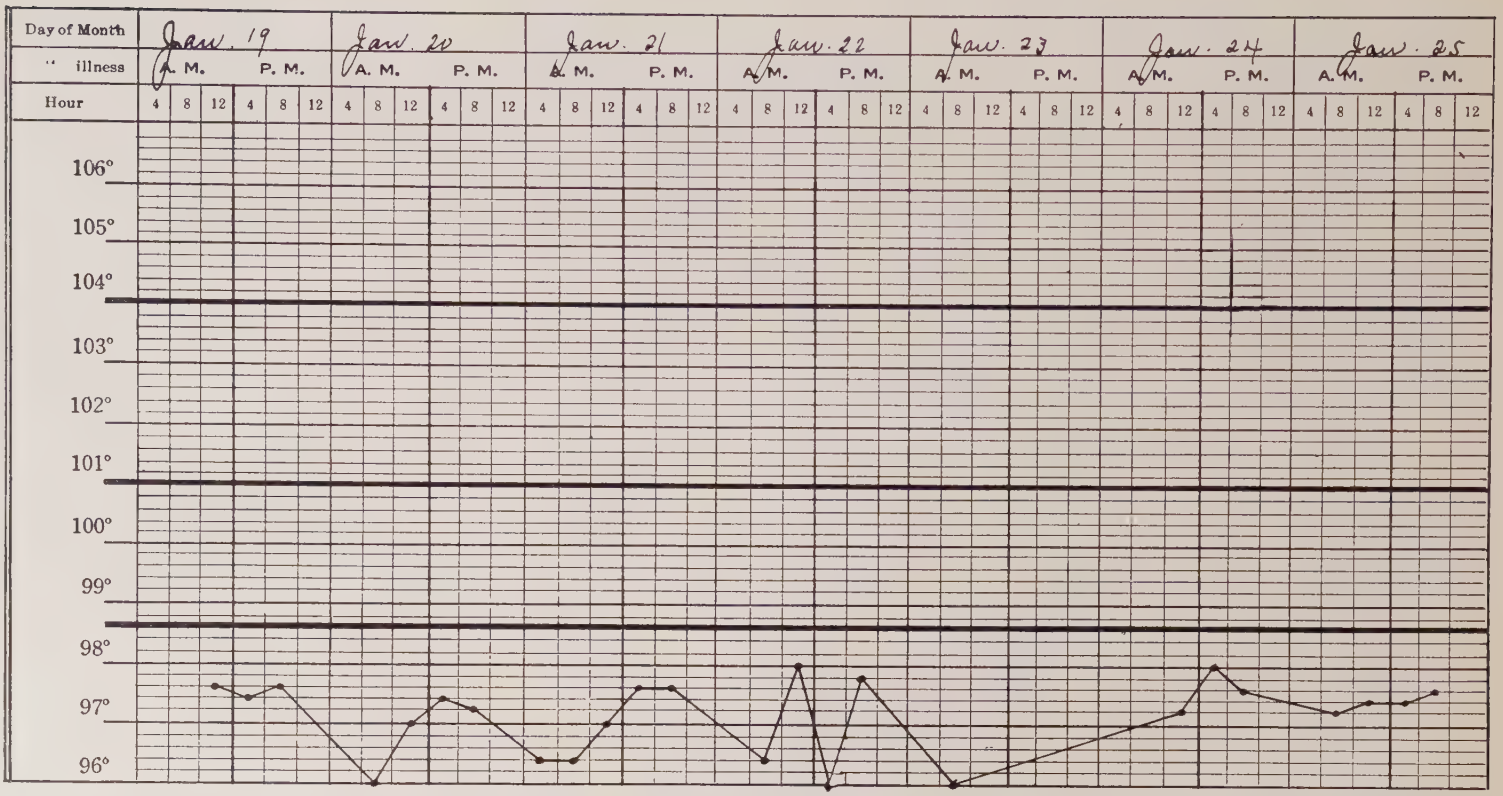

FIG. 115. Temperature-chart of a case of generalized seborrheic dermatitis, present summer and winter without remission for several years and caused apparently by sensitiveness to heat. Note that the temperature is almost constantly subnormal. This was typical of the periods in which the eruption was active. Through heat or effort the patient could be made definitely worse. (See also, Figs. 116, 117, 118.)

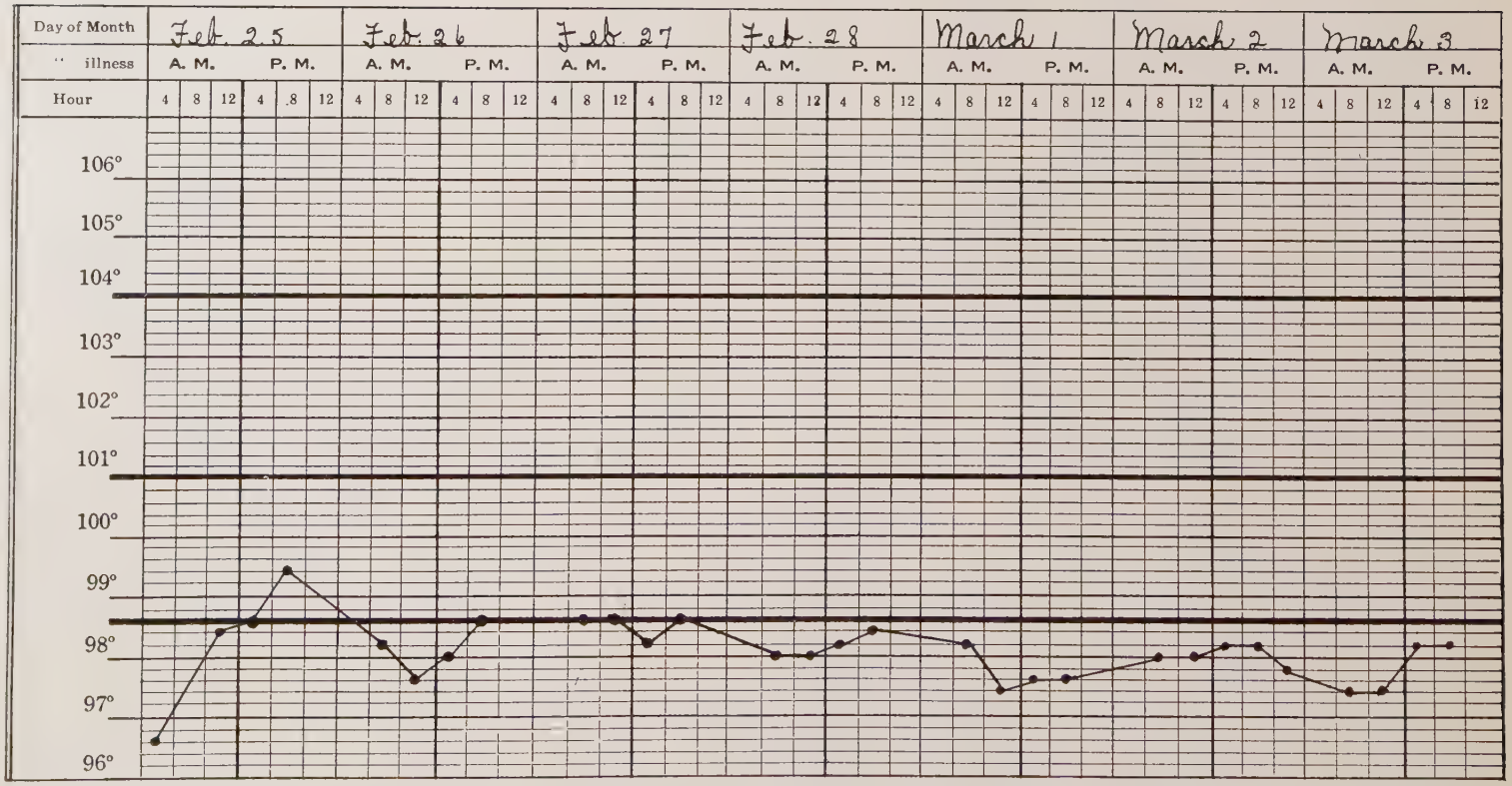

FIG. 116. Temperature-chart of a case of generalized seborrheic dermatitis (see also, Fig. 115). Note the results obtained through the use of heroic doses of *B. coli*, designed to raise the body-temperature to a higher level, frequently above normal. The eczema also completely disappeared.

It is occasionally observed that the metabolic rate is abnormally high and can be reduced by the application of cold to the skin. Strange to relate, a reduced rate frequently rises after the application of cold to the skin. In many cases, heat and cold may have the same effect so far as change in the metabolic rate is concerned. In some cases, the metabolic rate seems remarkably unstable and varies more than in normal individuals.

FIG. 117. Case of generalized seborrheic dermatitis referred to in Figs. 115 and 116. Note the generalized dermatitis, appearing as darkness of the skin. Note, also, the loss of hair and eyebrows. The patient had for several years been a victim to chronic, scaly, weeping eruptions, which had constantly resisted therapeutic measures. This photograph was taken at a period when his temperature was running almost constantly subnormal and when the eruption was very active.

3. Hyperesthesia to the Sensation of Heat or Cold

A number of patients who react abnormally to heat or cold, have skin hyperesthesia to heat or cold. In fact occasionally the application of a degree of heat which would appear scarcely more than warm to a normal person, would cause such patients to feel as though they were burned or blistered. Or, in the case of cold hyperesthesia, an application which would scarcely cause discomfort to the normal person, might make the patient shudder with cold.

4. The Fact that the Symptoms Can Be Reproduced through the Appropriate Application of Heat or Cold and Can Be Prevented or Relieved by the Reverse Application

The views expressed in the present paper are based upon the fact that the symptoms can be reproduced under suitable conditions by the application of heat or cold, and can be relieved by the reverse

FIG. 118. Photograph of patient shown in Fig. 117, taken after the use of therapeutic measures which elevated the body-temperature toward, or a little above, normal. Note the lighter color of the skin, the reappearance of the hair and eyebrows after the relief from conditions, through improvement in body-temperature. At this time the basal metabolism was relatively normal.

application. A study of this sort cannot be made on mildly sensitive cases or on patients who give delayed reactions for the reason that in these, the results are not sufficiently outspoken to be convincing.

THE TERMS, HEAT-SENSITIVENESS AND COLD-SENSITIVENESS

The terms employed in this discussion can be used rather loosely and do not commit one to a theory. It would not be wise at the

Fig. 119. Temperature-chart of a patient with urticaria of four months' standing, caused by sensitiveness to heat. The eruption could be brought out immediately through the effect of heat or of effort. This patient, contrary to the rule, showed an endocrine disorder characterized by an abnormal length of legs and arms, and a metabolic rate, which on repeated examination, was grossly below normal. On four nearly successive days, the results were −42, −56, −46, and −62. After heating the arms and hands by immersion in water at 42°C. for five minutes, and after applying a nitrogen lamp to the chest for a few minutes, the metabolism could be raised nearly to normal: upon one occasion from −56 to +16; at another time, after an ice-rub, from −31 to −4; and upon still another occasion, from −62 to −9. Tests were made shortly after treatment was commenced with glandular extracts designed to raise metabolism, with such results as −9, +19, +9, and +19. These changes were associated with intense clinical relief. Note the irregular, unstable, subnormal temperature shown in the chart. Notice, also, in the photograph, Fig. 120, the total absence of signs of myxedema to account for the patient's metabolic rate.

FIG. 120. Photograph of patient referred to in Fig. 119, taken a few days after a period when his metabolic rate had been almost constantly grossly subnormal; upon one occasion as low as −62. Note the absence of signs of myxedema.

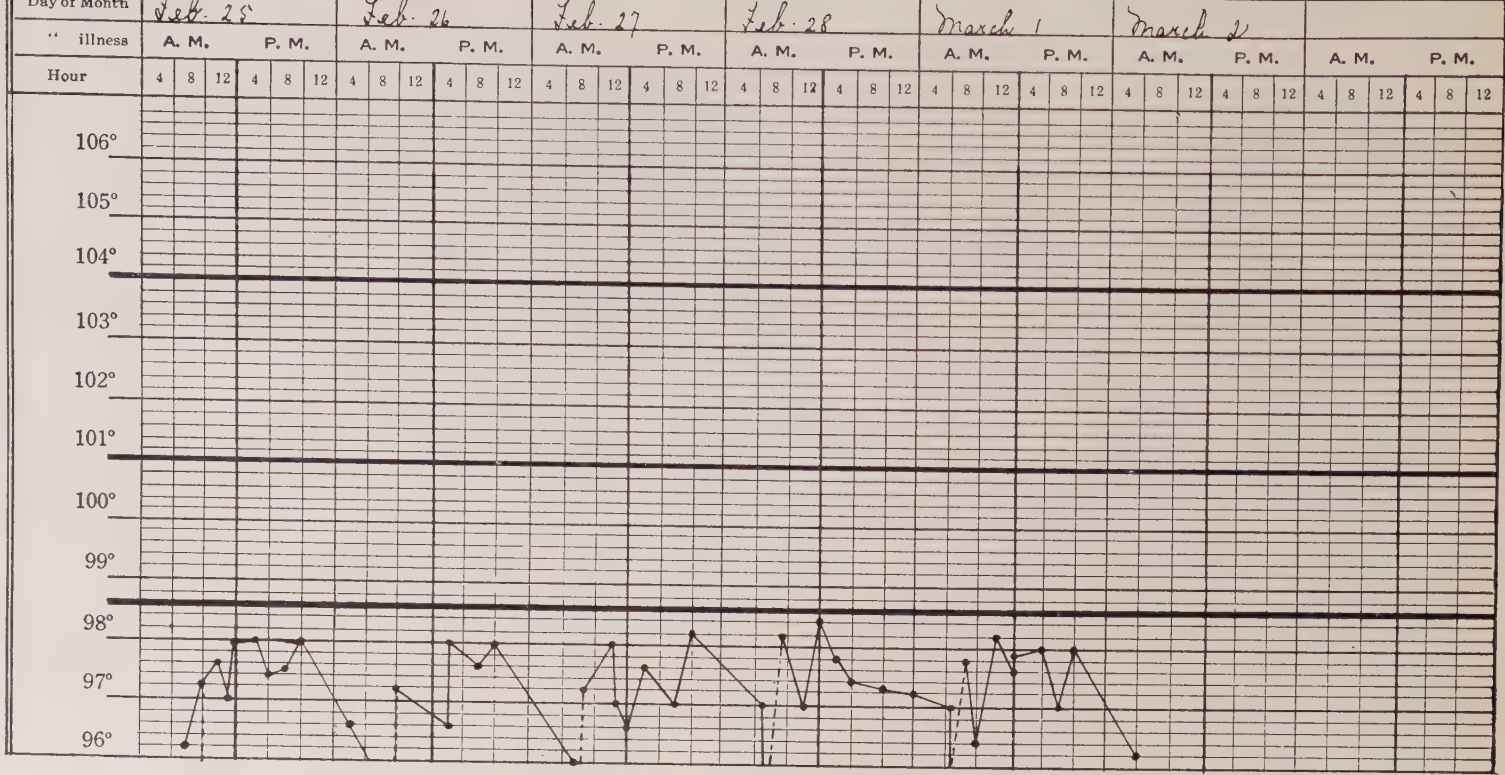

FIG. 121. Temperature-chart of a case of asthma caused by cold-sensitiveness. The rises shown by the dotted lines, were caused by a little exercise or by the application of heat in the form of a hot bath. If the temperature was raised each morning by this method, the patient remained comfortable throughout the day. If the temperature was not elevated, he would be subject to asthma upon being cooled or after prolonged quiet. Such attacks could be relieved immediately through exercise or the external application of heat if these measures were used soon enough. This patient keeps himself constantly comfortable through the effect of exercise, a hot bath, and a cool shower taken soon after arising.

present stage in the development of this study to use more specific terms or restricted definitions. It seems quite evident that among individuals who are sensitive to the effect of heat, cold or effort, there are a number of different underlying pathologic conditions which give rise to identical manifestations. In the present paper, therefore, the terms have been employed as follows:

Heat-Sensitiveness

Heat-sensitiveness has referred to patients who were apparently made ill by an increase in body-heat whether this was produced through reduced heat-loss, the external addition of heat, or through the effect of heat generated by mental or physical effort. Patients who responded to increased heat and effort most markedly after previous exposure to cold were considered, in spite of their history, as heat-sensitive cases. Furthermore, persons who responded most readily to heat or effort when breathing cold air were likewise referred to as heat-sensitive cases.

Cold-Sensitiveness

This term has referred to patients who were made ill by body-cold, whether produced by increased loss of body-heat or through the effect of reduced heat-production caused by mental or physical inactivity. Cold-sensitive cases occasionally reacted most pronouncedly in a hot environment, that is upon cooling off after exposure to heat. These, nevertheless, appeared to be cold-sensitive cases. Furthermore, patients sensitive to the effect of body-cold who reacted most markedly while breathing warm moist air, were called cold-sensitive cases.

Because of the fact that some heat-sensitive cases react after exposure to cold and cold-sensitive cases react decidedly after exposure to heat, and inasmuch as many cases react most strongly to internal heat if subjected to surface cooling and vice versa to internal cold if subjected to surface heat, it might seem simplest in a large proportion of cases to refer to the condition as combined sensitiveness or to classify it under the still less committal term, "thermal sensitiveness."

DIAGNOSIS

The diagnosis of thermal sensitiveness is not difficult. The history is important: that is, a history of symptoms induced by heat or

effort, or by cold and inactivity, and relieved by the opposite conditions. Patients can then be tested with heat, cold, and effort so that their symptoms can be reproduced directly under observation. This tends to make the diagnosis objective.

In heat-sensitive cases the procedure consists of immersing the hands and fore-arms in a water-bath at 42°C., or by the application of the heat of a large nitrogen lamp to the chest and arms or by diathermic currents. In cases of suspected cold-sensitiveness, the patient immerses the arms and hands in a water-bath at 15°C., or the arms and chest are rubbed with ice. If the above treatment does not produce the symptoms, further tests can be made in heat-sensitive cases by trying simultaneously the effect of heat and physical exercise by placing the patient in a steam-room and having him exercise.

For the testing of combined sensitiveness to heat and cold, a hot lamp can be applied to the chest and simultaneously a large pack filled with cracked ice can be applied to the face in such a way that chilled air can be inhaled. Or, an effort can be made to reproduce the symptoms by having the patient exert himself physically while in a refrigerator breathing chilled air. The reverse application is simpler—that is, the rubbing of the chest, arms, and back with ice while the patient is breathing air through a warm, moist pack on the face.

These tests can cause coryza, bronchitis, or pneumonia if applied too severely. But those complications are prevented when the reactions are controlled by a reversal of the applications.

TREATMENT

The treatment of patients highly sensitive to body-heat and effort is likely to be a serious problem. The treatment of patients sensitive to body-cold is likely to be successful.

Treatment of Heat-Sensitiveness

Patients extremely sensitive to heat should avoid effort unless they can be adequately cooled. They should avoid situations in which they are likely to be overheated. They are likely to do best in a dry, cool climate. Even a dry, warm climate is better for them than a cool, humid climate. Dry air makes body cooling easier. Heat-sensitive patients can stand more effort in a dry atmosphere than

in a humid atmosphere. It may be necessary for them to seek an environment and a career which will enable them to lead a quiet life in a dry atmosphere. This may be the best solution in highly sensitive cases.

In moderately sensitive cases, relief can frequently be obtained through attention to general health and through the use of agents which are designed to keep body-temperature running at a higher level. A common-sense practice of medicine is useful in the less severe cases. Since a large proportion of persons react most markedly when their body-temperature is the lowest, the avoidance of high grade subnormality in temperature is important. Many cases are definitely benefited through the effect of fever. A febrile disease almost always gives temporary, and frequently prolonged, relief. Fever can be induced artificially by the subcutaneous or intravenous injection of colon bacilli. By the use of this method, with gradually increased doses, continued for a period of from one to several weeks, to a point of producing frequent febrile reactions, the writer has obtained clinical relief for several desperately afflicted patients who had been ill for a number of years. The intravenous use of colon bacilli is likely to bring on a very quick febrile attack even if given in doses as small as 10,000. Although the author has had no unfortunate results with this form of therapy, he considers that the subcutaneous use of colon bacilli is much safer. The treatment must be pushed boldly, however, to secure successful results. It is the author's opinion that some of the therapeutic results which follow the use of autogenous vaccines, peptone, and milk, in the treatment of non-infectious coryza, asthma, eczema, and hives, are produced through the effect of these agencies in elevating body-temperature from subnormal toward normal or above normal.

Temporary relief can often be obtained through the use of hot or cold baths given when the patient needs them. Cold baths for the temporary relief of an attack may be effective within a few moments and may give a sensational result. Hot baths at midnight for the prevention of a drop in temperature from relatively normal to high grade subnormality during the early morning hours, may prevent such attacks. On several occasions the author has been able to avert early morning attacks through warming up the patient thoroughly by a hot bath at midnight. (See Fig. 121.)

Symptomatic remedies which are useful for such symptoms as

coryza, asthma, urticaria, and pruritus, are adrenalin, pituitrin, ephedrine, atropine, and the salicylates. Morphine and alcohol may be effective. The employment of the former is rarely justifiable. The use of acids is indicated where achylia is found.

Treatment of Cold-Sensitiveness

Cold-sensitive cases are much more fortunate than the heat-sensitive. In the first place it is much easier to avoid overcooling than overheating. Where persons are chilled, they can frequently relieve themselves through the effect of exercise. Cold-sensitive cases, like the heat-sensitive, tolerate temperature changes better in a dry than in a moist climate. Dry air, whether hot or cold, is easier for them to tolerate than humid air. They should be cautioned against undue exposure to cold.

Fortunately, patients can sometimes gain tolerance for cold through the use of frequent cold baths. This is often a most useful remedy in a proven cold-sensitive case. Occasionally one can obtain complete clinical relief in a cold-sensitive case through as simple a measure as having the patient take a cold bath each morning. Although prolonged exposure should be avoided, a cold bath for from fifteen to thirty seconds, frequently repeated, may suffice to give tolerance. Cold-sensitive patients are often hyperesthetic to cold. In this case, they may be unable to tolerate adequate exposure to cold during the early part of their treatment. After a time, they are likely to learn to enjoy exposure to cold.

Symptomatic remedies in the treatment of heat-sensitiveness can be used to advantage in the treatment of cold-sensitive cases. Moreover, if body-temperature is inclined to be subnormal, they can usually be benefited through the use of agents which raise temperature.

SUMMARY

In the present paper the writer discusses a series of relatively common illnesses which he believes are frequently caused by a disorder in the heat-regulating mechanism. These illnesses include heat-prostration, symptoms of the effort-syndrome, non-infectious coryza, asthma, urticaria, dermatoses, and other miscellaneous ailments.

The heat-regulating mechanism is very important and extremely

complex. For effectiveness it requires the co-ordinated action of many structures which control heat-production and heat-loss. Of the structures which seem important may be mentioned the cerebral centres which have a thermostatic effect upon heat-control; several hormones which effect both heat-production and heat-loss; histamine-like bodies which affect vascular tone; the three important cooling surfaces, namely, the skin, the mucous membrane of the nose, and the bronchial tubes; the structures which control the secretion of moisture upon the cooling surfaces; the structures which control the depth and rapidity of respiration and rate of blood-flow to the surfaces and to the active internal organs.

Under certain conditions this complicated mechanism becomes disordered at some point and, when so disordered, gives abnormal responses to sensations of heat and cold. Responses to heat and cold may then be inadequate to maintain ideal temperature, or they may be exaggerated, or in some cases perverted. Abnormal responses give rise more often, apparently, to pathological conditions than does any direct effect of an abnormality in temperature *per se* on the tissues.

Allergic reactions to foreign substances may give rise to symptoms similar to those of sensitiveness to heat or cold and may therefore add to the manifestations of heat- and cold-sensitiveness, or in some instances may cause sensitiveness of this type for the time being.

In many individuals adequate cause for heat- and cold-sensitiveness can be discovered. In others, frequently no pathological condition can be found except heat- or cold-sensitiveness itself. In such cases a history of an acute febrile disease is often found, just antedating the onset of the illness. It is generally stated in the text-books, and probably correctly so, that in febrile conditions the heat-regulating mechanism works at an abnormally high level so that responses to normal body-temperature simulate those normally caused by a reduction of heat and give rise to a retention of heat. In many instances, convalescence from an acute febrile disease is associated with a subnormal temperature for a varying period of time. It might be assumed, likewise, that during the period of convalescence from a febrile disease, the heat-regulating mechanism is frequently working at an abnormally low level, so that a response to normal body-temperature might simulate that normally caused by increased temperature and give rise to an unusually great loss of heat.

It seems quite possible that under certain conditions the abnormal level at which the heat-regulating mechanism works during a febrile disease, or during convalescence, is maintained and gives rise to abnormal responses to heat and cold for prolonged periods of time, and sometimes permanently. In many patients afflicted as above, symptoms caused by heat and effort are identical and in others, symptoms caused by cold and inactivity are identical. In patients such as these, the ailments of which they complain can usually be reproduced objectively by the adequate and suitable application of heat and effort or of cold and inactivity.

During reactions of the above types caused by heat- and cold-sensitiveness, many patients are hypersusceptible to infection. It is believed that this type of sensitiveness plays a part in the susceptibility of many patients to the spring and fall epidemics, and finally in the complicating infections which often follow febrile diseases, and in the predisposition of elderly people to respiratory infections.

The diagnosis of the condition can be made by studying the case-history and by practical tests.

The treatment of the condition depends upon the severity and the cause of the sensitiveness.

DISCUSSION

The following questions submitted to Dr. Duke before the Commission, together with the answers to them, are here reported verbatim.

Dr. Starr: I suppose everyone in the audience could rise and give examples to confirm the statements of the doctor. I do not wish to take much time but I should like to speak of a case that I have had under observation for about twenty years, that of a patient who is particularly sensitive in this way to heat. (I have recognized the symptoms.) But the particular symptom that this patient manifests is a swelling of the periphery of the body, not enough to call it an angioneurotic edema, but very manifest in the tightness of the rings on her finger. I have seen her go in a perfect state of comfort and health to a theatre and by the time the show was over, on account of the closeness of the air, I have seen her absolutely unable to take the rings off her finger. The actual swelling is visible.

I have noticed a great many individuals are sensitive in that way, indicating conditions that approach angioneurotic edema. It seems to me that the condition might be explained by a difficulty in this heat-regulating centre.

I also wish to state that this particular patient, who has been under my observation so long, is comfortable when she spends the winter in Egypt where the climate is extremely dry and yet is fairly warm.

Dr. Pollock: I should like to ask Dr. Duke whether in the cases which have a specific reaction, such as asthma, swelling of the nasal mucosa, and so forth, he could produce the specific reaction in each by the application of heat.

Dr. Duke: I produced these reactions in many of the heat-sensitive cases referred to, either by heat, or by heat and mental or physical effort combined, and I relieved them by the application of cold. In cold-sensitive cases symptoms were brought out by cold and relieved by heat or effort. The very things that make the heat-sensitive case sick, make the cold-sensitive patient better. I had one patient who had asthma caused by cold-sensitiveness, and he got into a fight. When the fight was over he had not only defeated his opponent but relieved his asthma. (Laughter)

Dr. Cobb: I should like to ask Dr. Duke whether we really ought to look upon these individuals as abnormal. Are not these reactions those that almost all of us have, and are they not, as a rule, within normal limits?

As a specific example, I am not an especially abnormal individual, but I am more or less neurotic. After I had read my recent contribution here, I had excessive sweating in the hands and in the axilla, trembling, and all that. I only want to bring this out because with our already overburdened nomenclature we do not wish to bring in new syndromes, if they are explainable as normal mechanisms that we all have. There are extremes which are outside normal, obviously, but might we not explain almost all of them by the one phrase, "vasomotor instability"?

Dr. Duke: To answer Dr. Cobb's question, these reactions that I have spoken of seem very often to be an exaggeration of a normal action, but they may be exaggerated many fold. For example, if one of my patients highly sensitive to heat were in your situation, he might have hives or asthma. They instinctively avoid heat and effort. You might call this "vasomotor instability," but "vasomotor instability" does not convey a very concrete idea. The terms, "heat-sensitiveness" and "cold-sensitiveness," convey a very definite idea.

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CHAPTER XXIV

THE RELATIONSHIP BETWEEN THE EMOTIONS AND THE CLINICAL MANIFESTATIONS IN THE INVOLUNTARY NERVOUS SYSTEM (AUTONOMIC IMBALANCE)

LEO KESSEL, M.D.

VISCERAL symptoms resulting from an acute emotion undoubtedly follow a pathway through the involuntary nervous system. The frightened individual may present tremor, tachycardia, hyperpiesis, diarrhea, pylorospasm, sweating, or any of the host of visceral disturbances, and no one will doubt that the pathway has been an emotional disturbance, a stimulation of the involuntary nervous system, a visceral manifestation.

No two individuals will respond to a given emotion in a manner exactly similar. Stated more technically, no two reaction pictures in the involuntary nervous system will correspond. At the point of a pistol, *A* may present tremor, tachycardia and blanching, *B* hyperpiesis and flushing, while *C* may develop pylorospasm or an acute diarrhea, and *D*, syncope. The clinical pictures present a wide diversity, though the fundamental physiological process is identical.

Despite the wide repertory of the reaction picture in different individuals, the same individual usually develops a very fixed reaction picture at different times and under different emotions. At the point of a pistol, if he should present the syndrome of flushing, tachycardia and tremor, for example, he would probably present the same reaction picture at an exciting movie or in an embarrassing position. So characteristic of an individual is his reaction picture that intimate friends will instantly recognize the reaction picture and know that there is an emotional crisis in operation. Such acute visceral crises usually afford no difficulty in diagnosis or treatment.

Individuals under prolonged emotional strain, however, may develop this reaction picture in a more or less chronic state. In fact, the visceral symptoms may either be out of all proportion to the emotional crisis, and overshadow it completely, or they may outlast the emotional crisis, and it is here that the visceral manifestations are

presented to the internist, and afford to him difficulties both in diagnosis and treatment. Usually by the time the reaction picture has been sufficiently established to warrant a visit to the internist, at least two complicating psychic factors make their appearance. First, the emotional disturbance being either overshadowed or else no longer operative, the patient develops an anxiety state, fearing that the subjective symptoms are manifestations of organic disease. Second, the reaction picture becomes conditioned in exactly the same way that a reflex may be conditioned, so that causal relationships are difficult to ferret out. The anxiety concerning organic disease causes a reactivation and often intensification of the reaction picture. The conditioning of the emotion creates the diagnostic difficulty.

Very often the patient will consult the physician complaining of the symptoms of the reaction picture, and withholding the story of the emotional strain. Specialists in particular are prone to focus on the organ that is the site of the subjective symptoms, and diagnose and treat the symptoms as manifestations of a local organic functional disturbance, thus cardiac neurosis or gastric neurosis. It has been the author's experience that this type of management increases the reaction picture by focusing the attention of the patient on the organ and adding to the anxiety.

The internist must be on the alert for the recognition of the reaction picture in eliciting the patient's history. As soon as he has convinced himself from his physical examination that there is present no organic disease, the wary physician will make inquiry as to a possible etiological disturbance in the emotional sphere. One need not be a trained psychiatrist. Usually a few pointed and sympathetic questions will open the flood-gates.

In the presence of organic disease, the reaction picture requires an evaluation in the relative sense. The patient with hypertension who has had cardiac pain will often complain of his symptom when he reads in his newspaper that a friend similarly afflicted has died. Here the reaction picture is a result of an anxiety in an individual who has a hypertension and a sensitized involuntary nervous system. If the symptoms are interpreted as manifestations of further damage to his circulatory system, and if the physician restricts the activity of the patient and gives him medication and a strict régime, that very treatment will foster the feeling of insecurity and imminent death, and often reactivate the symptoms. Again, the visceral manifestations

may be conditioned in an individual with organic disease, so that a woman who developed an acute Graves' disease during the Titanic disaster will suffer a reactivation of symptoms when she reads in her newspaper of the Vestris disaster. If treatment be instituted for the Graves' disease one adds to the emotional burden of the patient, whereas a recognition of the conditioning may lead to a striking therapeutic result.

The term "reaction picture" is used deliberately here. The terms "sympathicotonia" and "vagotonia," are avoided. The manifestations in the involuntary nervous system are never pure in the sense that either one or the other system is involved alone. Invariably there is a blending and it is for this reason that the term "autonomic imbalance" has been used for the clinical entity and reaction picture for the particular syndrome the patient may present.

Each day brings instances of the frequency and importance of the recognition and treatment of these disturbances of the involuntary nervous system, and while it is true that their recognition and unravelling require infinite tact and patience, some of the most gratifying therapeutic results have occurred in this group of individuals.

DISCUSSION

The following questions submitted to Dr. Kessel before the Commission, together with the answers to them, are here reported verbatim.

Dr. Cannon: The author spoke of emotion in very general terms, it seemed to me. There are features which he mentioned which I could recognize as characteristic of major emotions, as anger and rage; but, after all, love is an emotion. I wonder whether these phenomena that he described would be resultant of love, as well.

I think that when we discuss emotion we ought to specify the sorts of emotion we have in mind.

Furthermore, Dr. Kessel considered very generally the involuntary nervous system. The involuntary nervous system is composed of three parts. There is a sympathetic division, which I tried to define clearly yesterday, and two other divisions, which are not ordinarily called sympathetic, but parasympathetic or autonomic.

The cranial division, for example, has in it the third, the seventh and the tenth nerves; and when these representatives of the cranial division meet in any organ representatives of the sympathetic or mid-division of the autonomic, they are opposed in action, as a rule. The vagus causes inhibition of the heart; the sympathetic causes acceleration; and so on, throughout the whole series of organs thus innervated.

Then it was stated that the involuntary nervous system is brought into action in emotion. It is obvious that the cranial division and the sympathetic division cannot be brought into action simultaneously because they cannot work in opposite directions at the same time. It seems to me, therefore, that we have to analyze this situation more carefully than is indicated by merely a reference to the activation of the involuntary nervous system.

Occasionally statements are made which surprise physiologists. I wonder how it is possible to observe in a person who is subjected to an acute emotion the phenomenon of pylorospasm. As I understood it, the writer said that pylorospasm is one of the characteristics of an emotional response.

Dr. Kessel: I agree with most of what Dr. Cannon has said but I believe that we look at these things, one of us from the standpoint of the clinician, and one from the standpoint of the physiologist. However, I think that I could tell you how we determine the presence of pylorospasm, by relating the story which was told to me in my office three days ago.

A patient who has had a perfectly definite duodenal ulcer over a period of years, with periods of remission (and he has had the ulcer proven clinically, X-ray finding and all of the necessary clinical phenomena being present), came to my office after an interval of several months and said that his symptoms had returned but that they were not quite the same. He had the burning but he did not have the pain directly in relation to his meals. I said, "How are they not the same?"

"Well," he said, "I am conscious of my stomach and while I feel that I have this burning and while I occasionally feel a cramp-like sensation, it is not relieved by food, and it is not brought on by taking food at a definite interval after a meal, and I feel that it may be due to the fact that I have put up a large office building which is only 20 per cent rented."

There is also a great deal of X-ray evidence to show that pylorospasm is frequently of functional origin.

Dr. Cannon: I fear that there is a difference between the requirements of evidence for physiology and for clinical judgment.

Dr. Meyer: I should just like to bring out the point which Dr. Kessel, I think, is trying to show, namely, the necessity of different formulations for different purposes.

Is not Dr. Kessel's formulation that of the clinician who, by the very necessity of his work, has to summarize and to introduce into his clinical working terms certain facts, while the physiologist is in duty-bound to limit himself to his physiological possibilities?

Dr. Cannon calls for a question with regard to a difference between the physiological conscience and the clinical conscience. May I ask Dr. Kessel whether he does not want to urge upon us the importance of total-activity to the clinical conscience when we study the imbalance of the sympathetic and automonic system? Might not the total-picture as found by the clinician contain more of the truth for the patient than the physiological consideration would by itself?

It seems to me that by pointing the issue in the direction of the relative importance and scope of responsibilities and the kind of facts one has to deal with, there is a possibility of coming around to a common ground and mutual understanding.

CHAPTER XXV

CERTAIN CHARACTERISTICS OF THE CORTICAL INFLUENCE OVER THE SYMPATHETIC NERVOUS SYSTEM IN MAN[1]

RICHARD M. BRICKNER, M.D.

KNOWLEDGE of the existence and properties of a cortical neurone in man, exercising an influence over the sympathetic nervous system,[2] is of paramount importance, if one ever hopes to comprehend the full significance of this branch of the nervous system. The potentialities of such a neurone as a source of physiological inquiry, and of investigation into many types of mental disturbance, seem to be great. Yet, despite the fact that there is a large amount of evidence pointing to its presence, both in man and in other vertebrates, comparatively little attention has been devoted to it, and practically nothing is known about it. What understanding exists in regard to this question must, of necessity, have been gleaned from clinical sources; and hence it is fortunate that patients with various forms of nervous disease lend themselves very well to experimental study. That the cortex influences the sympathetic nervous system in cats, dogs and rabbits, has been established mainly by the experiments of von Eulenberg and Landois (11), von Bechterew (3), Gribojedow (14), Winkler (33), Woodworth and Sherrington (34), Cannon and Britton (8), and Bard (1). All of this evidence will be described later.

The purpose of the present paper is to bring together the evidence that relates to this subject, and to add some new facts which seem to establish unequivocally that, in the human brain, the cortex has a specific influence over the sympathetic nervous system. It will also be shown that, as far as cortical control and the general principle of the release phenomenon are concerned, the sympathetic nervous

[1] From the College of Physicians and Surgeons, Columbia University, New York.

[2] The term sympathetic nervous system is used here according to Langley's definition (24). It refers to that part of the autonomic system which is concerned in the thoracicolumbar outflow.

system acts under precisely the same laws as do the somatic motor and sensory systems.

The evidence upon which these conclusions depends has been gathered from experiments on the pilomotor behavior of three patients, —two cases of left hemiplegia, and one of partial interruption of the spinal cord. Patients 1 and 3 were seen at the Vanderbilt Clinic of the Medical Center of New York,[3] and Patient 2 in the office of Dr. Frederick Tilney.

SUMMARY OF CONDITIONS IN THE THREE PATIENTS

Case 1. H. B., a man forty-two years old, suddenly collapsed one year before he was seen at the Vanderbilt Clinic, while leaving his home early in the morning. He did not lose consciousness. He had had increasingly frequent headaches and vertigo for five months prior to this episode, but otherwise he had been perfectly well. Since the stroke he has had a moderately severe left hemiplegia, including weakness of the left facial muscles which has slowly but steadily improved. For the first four hours only, he had difficulty in speaking. Since the stroke he has cried more readily than before, though he had always been emotional, he said. His examination revealed a marked weakness of the left arm and leg, with slight spasticity of the arm, slight left facial weakness, greatly increased deep reflexes on the left side, a left Babinski, and absent left abdominal reflexes. Babinski's trunk-thigh sign was present on the left. There were no sensory changes. The blood-pressure was 134 systolic, 90 diastolic. The blood Wasserman test was negative. The left extremities were usually mottled, and were colder than those on the right. A diagnosis of thrombosis of the right ascending frontal artery was made.

Case 2. M. B., a man thirty-eight years old, had suddenly collapsed one and a half years prior to his visit to Dr. Tilney. He also had not lost consciousness. He, too, had difficulty in speech at the beginning, which persisted for about two weeks. Since the stroke he has had a severe left hemiplegia with slight left facial weakness. He showed extreme spasticity of both left extremities, with marked paralysis, highly exaggerated deep reflexes and the Babinski reflex, absent left abdominal reflexes and a slight left facial weakness. There were no sensory changes. The blood Wasserman test was negative. The left extremities were usually mottled and colder than the right. He had auricular fibrillation and mitral stenosis, and it is believed that his accident was caused by an embolus from an auricular mural thrombus.

Case 3. J. I., a man twenty-nine years old. Eleven weeks prior to his visit to the clinic the patient was stabbed in the back with a penknife. The knife had partially injured the spinal cord on the right side, at the level of the fourth dorsal segment. Whether the lesion of the cord was a contusion or a section was in doubt, but, as will be seen, the conclusions of the present study are the same either way.

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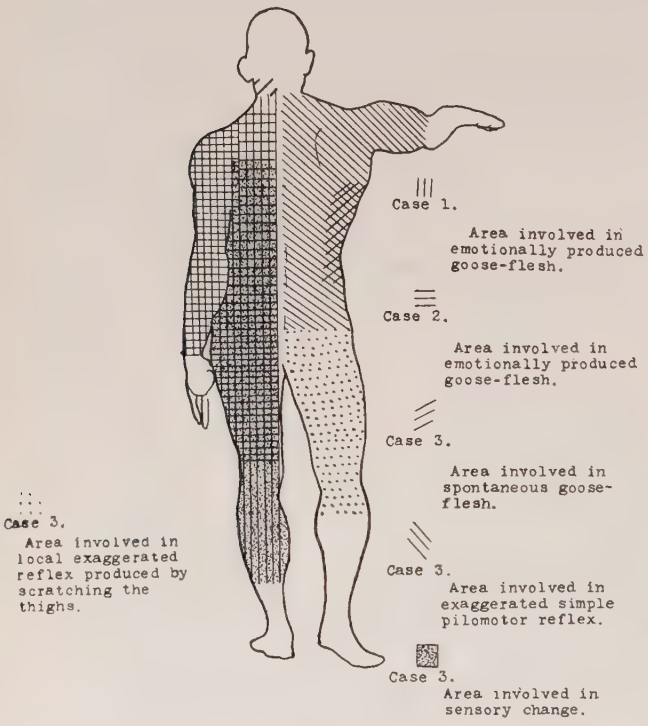
[3] The author wishes to express his indebtedness to his lamented friend, Dr. A. Philip Zemansky, for his invaluable assistance in the study of the first patient.

He had a partial Brown-Séquard syndrome. His right leg was moderately spastic, its deep reflexes were greatly exaggerated, there were right Babinski and Chaddock reflexes with fanning, and the right abdominal reflexes were greatly diminished. On the left side, from the level of the lesion down, the pain sense was greatly, and



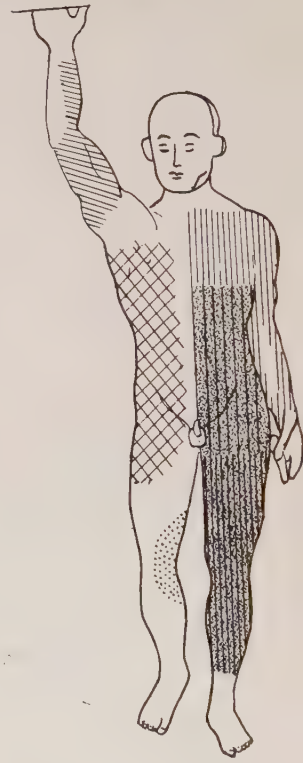


FIG. 122 FIG. 123

FIG. 122. Diagram of the areas involved in the pilomotor reactions and in the sensory changes.[4] Posterior view, Cases 1, 2 and 3.

FIG. 123. Diagram of the areas involved in the pilomotor reactions and in the sensory changes. Anterior view, Cases 1, 2 and 3.

the temperature sense moderately, diminished. The interference with sensibility was the most marked just below the level of the lesion. Passing down the body and lower extremities, the alteration gradually diminished. The vibratory

[4] Figs. 122–125, lines closely spaced signify a more intense reaction than lines widely spaced. The identification signs given in Fig. 122, apply also to Figs. 123–125.

sense was moderately lessened on the left great toe. Otherwise, the sensibility of the lower third of the left leg, and of the left foot, was normal. There were no other sensory abnormalities. The left leg, but not the foot, was somewhat mottled, and was usually colder than the corresponding zones on the right. Severe obstipation, but no bladder disturbances, followed the injury. The sensory changes are shown in Figures 122 and 123.

All of the patients were rather hairy individuals, so that the opportunities were good for examining the behavior of the pilomotor mechanism. Patients 1 and 2 were each seen between ten and fifteen times; Patient 3 was observed five times.

TECHNIQUE OF ELICITING THE PILOMOTOR REACTIONS

The patients were always entirely nude, and were usually placed in a standing position, avoiding all contact with anything except the floor. The main light came from a window, and the patients could revolve themselves so as to change the distribution of shadows when necessary. Strong incandescent lamps were also employed, to bring out additional shadows. For certain specific purposes, such as the placing of ice against the soles of the feet, it was necessary to have the patient lie on his back.

1. The Simple Pilomotor Reflex

By the term simple pilomotor reflex, the author refers to the pilomotor reaction mediated through the simple reflex arc, segmentally and without the involvement of any long ascending or descending tracts within the central nervous system.

The method of eliciting the simple pilomotor reflex, which is most convenient for the present purposes, is a gentle scratching of the middle of the back of the neck or of the back, with a dull point attached to a handle. A steel pen in its holder is a very suitable instrument. The pressure may or may not be great enough to produce pain. The stimulus was applied to the actual midline as well as the latter could be determined. Sometimes the midline of the back of the neck or of the back was lightly rubbed with the edge or point of a small piece of ice. The edge of a towel was also occasionally employed for gentle tickling of the hairs of the back of the neck. Scratching with a point was the most satisfactory method because that stimulus could most easily be confined strictly to the midline. A towel is likely to touch adjacent parts, and the trickling drops of water from melting ice may run down either side, and themselves serve as a stimulus.

2. The Pilomotor Response to an Emotional Stimulus

The patient was not permitted to change the position of his body nor to touch anything while the test was proceeding. The pilomotor

reaction was elicited by reminding the patient of, or getting him to talk about, some experience or story which moved him. During all the observations an effort was made to keep the lights and shadows as nearly the same as possible. All parts of the body could be observed, either by having the patient revolve himself, or by the examiner's circling around him.

THE PILOMOTOR REACTIONS IN THE TWO CASES OF HEMIPLEGIA

1. Spontaneous Pilomotor Manifestations

No spontaneous pilomotor hyperactivity was observed at any time.

2. The Simple Pilomotor Reflex

The pilomotor reflex, elicited according to the technique just described, was always identical on the two sides, in promptness of appearance, intensity and duration, as far as could be determined by the unaided eye. The reflex usually produced a moderate amount of goose-flesh, but no noticeable hair-erection. The areas involved in a reflex evoked by the stimulation of the middle of the back of the neck, were the upper part of the back and the posterior surfaces of the arms.

3. The Pilomotor Response to an Emotional Stimulus

Upon such stimulation, the goose-flesh always appeared more promptly, was much more intense, and persisted longer on the hemiplegic than on the normal side. Accompanying the display of goose-flesh on the hemiplegic side, there was a marked erection of the hairs of the upper extremity. These observations, as well as those on the simple pilomotor reflex, were confirmed by Professors Strong, Pike, Elsberg and Cornwall.

H. B. (Patient 1) had been somewhat more easily moved to tears, though not to laughter, since the occurrence of his hemiplegia. News of either a sad or a happy event touched him profoundly. He was frequently much stirred on reading, in a newspaper, of a suicide or accidental death. He was considerably swayed when he thought about or told the story of his stroke, of some of his experiences at the front in the Russo-Japanese War, or of his little daughter's recent promotion in school.

The difference in the degree of the reaction was first noticed on the patient's initial visit to the clinic, when, as he was standing nude,

ready to be examined, he was questioned regarding a point in his history. As he commenced to speak, his left (hemiplegic) arm became peppered with goose-flesh, and the arm-hairs erected themselves considerably. The right arm displayed a very moderate reaction, with some goose-flesh, but no definite hair-erection. Immediate examination showed that the same effect was evident on the entire back, including the neck, in the loin, and, to a lesser extent, on

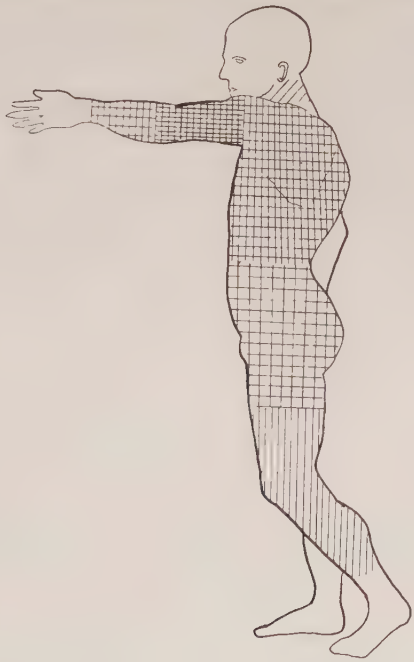


FIG. 124. Diagram of the areas involved in the emotional pilomotor reactions of Cases 1 and 2. Side view.

the left lower extremity near the junction of the lower and middle thirds of the leg. The implicated zone is shown in Figures 122, 123 and 124 and a photograph of the reaction is given in Figures 126 and 127. This observation was repeated many times. The patient would be asked, on various occasions, separated by from three days to a week, to tell the story of his attack or of his battle experiences. The hair would commence to stand up, and the goose-flesh to rise, as soon as he started to talk; or, if his speaking were slightly delayed, the

pilomotor response would reveal itself in advance of the actual speech, evidently with the inception of the thought which moved him.

One day, after the observations had been going on for about five weeks, he told of the promotion of his little daughter in school on the previous day; the onset of this talk was accompanied by a massive pilomotor effect, which, again, predominated vividly on the hemiplegic side. This experiment was also repeated many times.

That the effects were not due to a decreased temperature of the hemiplegic side is shown by the fact that they were just as striking if the skin of the left side was kept warmed under a hot lamp throughout the experiment.

The reaction usually persisted for about twelve seconds after the initiation of the thought which served as the stimulus. As the story continued, it would sometimes reappear for a few seconds. Immediate repetition of the same story evoked the same phenomenon each time, but with diminishing vigor. It never disappeared altogether. The same narration several days later resulted in a pilomotor response of renewed strength, on the first five or six occasions, but reiteration, thereafter, even after a week's rest, produced a considerable lessening of the intensity and duration of the reaction. However, at the time when the story of the stroke was beginning to weaken in its effect, the experiment with the battle tale was started, and the results were fully as pronounced as they had been before with the first stimulus. When the second story was commencing to be less effective, the daughter's promotion occurred, and its relating produced a tremendous response. The power of this narrative to give a strong effect also diminished after five or six repetitions.

When the patient was under the emotional sway of one of his stories, he always tended to move his arms and legs, and he had to be told repeatedly to stand still.

M. B. (Case 2) gave the same type of pilomotor response to emotion. He was not only a much more intelligent man, but was somewhat less easily moved. He was the most excited when thinking of kindnesses he had received at the hands of a certain individual. While reflecting on this episode even without talking about it, or actually describing of it, the patient displayed vivid symptoms of hair-erection and gooseflesh, which involved the whole left side of the back, all surfaces except the anterior of the left arm and fore-arm, the left loin and the left thigh. The area involved, is shown in Figures 122, 123 and 124.

There was a very moderate display of goose-flesh, but no hair-erection on the right side of the back or the posterior surfaces of the right upper extremity. The same phenomenon was elicited when the patient told of the abuse of his children by his wife. This man, like the other, always tended to move his whole body when in the sway of an emotion, and he had to restrain himself volitionally in order to remain still. Ordinary wide movements of his normal arm, however, when not accompanied by any display of feeling, did not bring forth any pilomotor reaction.

This patient, like the other, produced gradually weaker pilomotor responses when the same stimulus was used again and again on any one day. The same story, retold at intervals of from four days to a week, showed a steadily diminishing recovery of its strength the first four or five times, after which the pilomotor responses were still definitely greater on the hemiplegic side, but the striking character of the difference in intensity and duration was lost.

When the first two stories had become enfeebled as stimuli, the patient told of his personal correspondence with a man of great distinction who had a similar physical infirmity. The resulting goose-flesh on the hemiplegic side again appeared sooner and was far greater in intensity and duration than that on the normal side, and was accompanied by an erection of the hairs that occurred nowhere in the normal areas except in the down of the loin. The power of this stimulus also deteriorated after five or six separated repetitions.

During one examination, at this point, the patient was asked whether the presence of a female physician would be objectionable. He declined in embarrassment, with a pilomotor response which was very highly exaggerated on the affected side. A repetition of this incident as a story four days later gave a definite but noticeably diminished reaction.

4. Reaction to Adrenalin

Patient 1. The subcutaneous injection of 0.7 cc. of adrenalin into the right arm, produced no noticeable affect in the skin on any of three occasions.

Patient 2. Because of the cardiac condition, no drugs were administered.

5. Sweating Phenomena

No spontaneous hyperhidrosis was observed in either patient, though it was looked for in both.

Patient 1 received 0.01 gr. of pilocarpine hydrochloride on two separate days, under the skin of the right arm. Generalized slight sweating occurred on both sides of the trunk; it was definitely greater on the hemiplegic side.

Summary and Conclusions Regarding the Two Cases of Hemiplegia

In two cases of ordinary left hemiplegia, when the patients passed through an emotional experience, pleasant or unpleasant, large areas broke out into goose-flesh, which appeared sooner, was more intense and persisted longer on the hemiplegic than on the normal side; the hemiplegic side also showed pronounced hair-erection, which was rarely, if ever, present on the unaffected side except in the down of the loin of Patient 2.

Simple reflex pilomotor activity, elicited by scratching the middle of the back, or the back of the neck with a point, was identical on the right and left sides.

That the production of this difference in behavior between the pilo-erector muscles of the two sides is not secondary to local changes in the skin—relating for example, to temperature or blood-supply—is demonstrated by the fact that the simple pilomotor reflex, elicited by stimulating the skin with a point, was the same on both sides. Moreover, the hemiplegic side of Patient 1 was kept under a hot lamp throughout one of the experiments. The lack of response to an injection of 0.7 cc. of adrenalin, also points to an absence of local susceptibility to stimulation of any part of the peripheral sympathetic neurones. The result, then, must depend upon a change in some part of the sympathetic nervous system, caused by the lesion which produced the hemiplegia, and it is evident that that change can be nothing else but the interruption of a neurone passing through the internal capsule. That the excessive pilomotor activity is not due to a lesion near the internal capsule, as in the corpus striatum or in the thalamus, but must depend upon a capsular lesion, will be shown after the discussion of the spinal cord case.

That neurone probably arises in some part of the cortex, and, traversing the capsule in company with the pyramidal fibers, must pass to

some lower part, probably of the dienecephalon, there to act upon what have come to be known as the sympathetic nervous centres. The parts which are those most probably impinged upon, in the light of present knowledge, are the hypothalamus and the caudoventral and perhaps the medial parts of the thalamus. Many experimenters, Winkler (33), Karplus and Kreidl (18–22), in particular, have observed definite sympathetic motor effects upon stimulating the hypothalamus in rabbits and in cats. Bard (1) has further defined the region, by noting the emotional behavior of cats after ablation of the hemispheres and striate bodies. Under these conditions, the animal can easily be provoked to undergo what Cannon and Britton (8) have denoted as sham rage. Sham rage consists essentially of the erection of the hairs in many parts, sweating on all the paws, pupillary dilatation, a peculiar cry, and furious motion of the extremities. The last point may be related to the constant tendency of both of the hemiplegia patients to move their limbs when they were excited. Bard made repeated thin transections caudally, and found that the typical reaction persisted only down to the removal of the caudal half of the hypothalamus, and of the most ventral and caudal fractions of the corresponding segments of the thalamus. The dorsal medial portion of the thalamus has also been invoked (Müller (27)).

Through the literature of many decades runs a thread of convincing evidence that the forebrain of man gives rise to a nerve-controlling sympathetic centre lower down. Raymond (30) attributes to Bichat a case of hemiplegia with facial hyperhidrosis of the paralyzed side. Probably the first to focus attention on the now well-known vasomotor and temperature changes, as well as the somewhat less prominent sudoral changes, in hemiplegia, was Chevalier (10). In his thesis, in 1867, he pointed out that the difference in temperature between the two sides of a hemiplegic patient varies directly with the degree of completeness of the paralysis. In 1876, Nothnagel (28) described his often-quoted case of hemiplegia, with increased warmth and redness of the involved side of the face, and epiphora from the same eye. The man also had miosis, enophthalmos and a narrowing of the palpebral fissure on the hemiplegic side. However, there is nothing to show that these changes did not antedate the hemiplegia. Von Leube (25) quotes Charcot and Nothnagel as stating that in hemiplegia there may be an increase in temperature, a reddening of the skin, edema and increased sweating on the hemiplegic side. Féré (13) in 1888, again

pointed to the differences in temperature between the right and left sides of persons with hemiplegia; he stated, also, that the blood-pressure is decidedly lower (100 to 150 mm.) on the affected side. In 1899, Parhon and Goldstein (29) described several cases of hemiplegia. In one, with pseudobulbar paralysis, there was marked edema of the affected hand. They also administered pilocarpine to thirty cases of hemiplegia,—in eight, the resultant sweating was equal on the two sides, but the sudoral reaction preponderated on the hemiplegic side in the remaining twenty-two. Bikeles and Gerstmann (5), in 1915, reported eleven cases of bullet injury to the "psychomotor" region of the brain, with marked disturbance of the finer hand-movements, with or without sensory changes, with varying degrees of hemiparesis, and with or without spasticity. Six of them showed spontaneous sweating on the affected side. All the patients sweated more profusely on the involved side after receiving pilocarpine. These investigators refer to Senator's case (31), in which an abscess was found in the right hemisphere at postmortem examination; the patient had had spasticity and ataxia, with sweating of the left arm. Zenner and Kramer (35) refer to a case of endothelioma compressing the left parietal lobe, on which they operated in 1909. During manipulation of the tumor in both the first and second stages of the operation, the pulse practically disappeared from the right wrist, though it was easily palpable in the left. The right wrist gave a good pulse at all other times. Karplus (17) tells of some instances of gunshot wounds of the brain, with light, heterolateral hyperhidrosis. It is interesting to note that he concludes that the cortex contains no sympathetic centres, but merely exercises a general control over the thalamus. In substantiation, he points to the lightness of the hyperhidrosis in these cases, as contrasted with the greater effects following lesions of the spinal cord, of the cervical sympathetic nerve or of the peripheral nerves. Müller ((27), pp. 371, 372) states that in the first hours after a hemiplegia there may be vasoconstrictor paralysis and an increase in dermographia rubra on the affected side; that in cases of long standing, the latter sign may persist and "dermographia pilomotoria" may be seen.

There is, finally, Maxwell's rather remarkable case of voluntary hair-erection (26). The subject, who was normal in every other respect, could erect the hairs voluntarily in all parts of the body where goose-flesh usually appears under ordinary circumstances. He

claimed to be able to accomplish this through pure volition, without recourse to memories of exciting or painful experiences. Instances of voluntary control of the heart-beat have been reported, and volitional dilatation of the pupils is sometimes encountered. The author is acquainted with an intelligent man who can gaze into a bright light and cause his pupils slowly to dilate. Whether or not these bizarre phenomena depend upon conjuring up exciting images, they demonstrate, at all events, that the cortex has an influence over the function of the sympathetic nervous system.

A considerable amount of evidence from animals under experiment, also demonstrates the existence of a cortical sympathetic neurone in cats and in rabbits. Brown-Séquard in 1875 (6) was evidently the first to observe visceral responses to cortical stimulation. Scorching the cortical surfaces, in rabbits and dogs, produced a narrowing of the homolateral pupil, with lid-drop, and sometimes a rise in the temperature of the homolateral ear. A year later von Eulenberg and Landois (11) destroyed an area close to the sulcus cruciatus in dogs, and discovered a rise in temperature of from 1.5° to 7°C. in the contralateral extremities. The stimulation of the same zone caused a contralateral cooling of from 2° to 6°C. Von Bechterew (3) was able to produce a secretion of tears, in cats, by stimulating a part of the gyrus antecruciatus. Simultaneously, the pupil was widened and the eye protruded. The effects were always most marked on the opposite side of the body. Stimulation of the anterior part of the gyrus sigmoideus gave rise to contralateral sweating. The stimulated area was then removed, and subsequent injection of pilocarpine produced a much diminished secretion of sweat on the heterolateral side. He quotes Gribojedow (14), who confirmed much of his work. Stimulation of neighboring areas also caused a flow of milk from the breasts (4). Von Bechterew also quotes Karpinski (16), who produced an increased stream of urine from the ureters, mainly on the heterolateral side, upon stimulation of the gyri sigmoidei and precruciati. Winkler (33) using rabbits, confirmed von Bechterew's results in regard to sweating, except the part of the experiments involving the essential heterolaterality of the response. But he found that a more excitable portion of the cortex than von Bechterew's and Gribojedow's zone was the basal, anterior part of the frontal lobes. He observed, moreover, that cortical stimulation caused more profuse sweating in the fore- than in the hind-part of the body,—a point that will be touched upon again later.

Bazett and Penfield (2) have demonstrated clearly that in decerebrate cats the normal body-temperature regulating-control is lost. Their animals also showed a glycosuria. The hyperglycemia that follows decerebration was well studied by Bulatao and Cannon (7) in 1925.

While the thermal, vasomotor and sudoral changes so well known in hemiplegia patients bespeak an alteration of a hemispheral sympathetic neurone, they do not seem to indicate whether that neurone

FIG. 125. Diagram of the area involved in spontaneous goose-flesh. Side view Case 3.

serves merely in a transmissory capacity, or whether it also has an inhibitory function. The overactive pilomotor phenomena described in the present report, are clear illustrations of Jackson's release phenomenon, and show that an inhibitory influence has been lost.

The evidence so far adduced, therefore, proves that some part of the cerebral hemispheres not only exercises control over the function of the sympathetic nervous system, but that this influence is an inhibitory one.

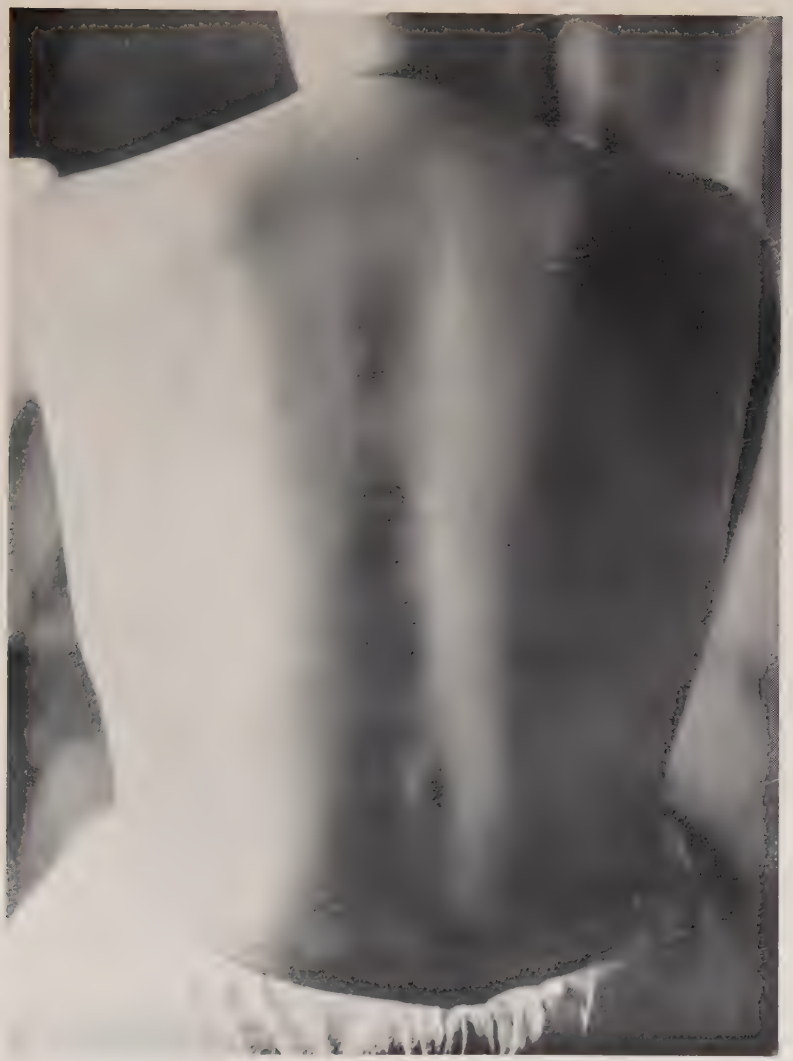


FIG. 126. Case of partial spinal cord interruption. The exaggerated simple pilomotor reflex. The line of the scratch can be seen.

THE CONTRASTING EFFECTS FROM A PARTIAL INTERRUPTION OF THE SPINAL CORD

Case 3 (J. I.) had a partial interruption of the right side of the spinal cord, at the fourth dorsal segment, with a partial Brown-Séquard syndrome.

Fig. 127. Case of partial right spinal cord interruption. The photograph shows the zone of spontaneous pilomotor activity on the left side of the neck.

1. Spontaneous Pilomotor Effects

There was spontaneous overaction of the pilomotor muscles of the right loin, most of the time. It was manifested by a light covering of goose-flesh in that region, extending from the axilla to a point just below the hip joint when the patient stood, nude, unstimulated. A small band on the left side of the neck, two inches wide and extending from the posterior midline to about the angle of the jaw also frequently showed such spontaneous goose-flesh. These areas are indicated in Figures 122, 123 and 125.

2. *The Simple Pilomotor Reflex*

In his invaluable monograph, André Thomas (27) has carefully described the exaggeration of the pilomotor reflex below the level of

FIG. 128. Case of left hemiplegia (H. B.). The patient was telling of the promotion of his little daughter in school. There is a considerable amount of goose-flesh on the back, left (hemiplegic) side; while the reaction on the right side is very slight. In examining this photograph, it is necessary to compare the edges of the long shadows on the respective erector-spinae muscle-groups of the two sides, since it is practically impossible to photograph goose-flesh excepting at the edge of a shadow.

the lesion in a large number of spinal cord injuries. The present instance is reported merely for the sake of contrast with the hemiplegia cases.

The reflex was greatly exaggerated on the right side, in a zone occupying the back from the lower border of the trapezius to the crest of the ilium; laterally it extended from the dorsal to the ventral mid-line. Though the reaction in front of the anterior axillary line and and on the anterior aspects of the arm and fore-arm was slight, it was greater on the right than on the left. The entire right upper extremity was included, except the hand. The strip on the left side of the neck which showed spontaneous hyperactivity was also involved. The erectile power of the nipple was not affected. There was slight exaggeration of the reflex on the right buttock and thigh. These areas are indicated in Figures 121, 122 and 125, and the reaction is illustrated in Figure 128.

The most pronounced effects were obtained by stimulating the middle of the back, near the lesion. The response became less and less marked in direct relation to the distance of the stimulus from the lesion. Stimuli applied directly to the chest or abdomen produced greater responses in the front than could be elicited by scratching the back of the neck.

In order to bring out the difference between the reactions on the right and left below the crest of the ilium, it was necessary to stimulate in the crevice between the buttocks, or to scratch the respective buttocks or inner surfaces of the thighs locally in quick succession, or to place ice against the soles of both feet simultaneously. While the difference between the right and left responses on the buttock and thigh was definite, it was never so great as that in the upper part of the body.

Pilomotor Reaction to Emotion

The patient was only a fairly excitable person. The story of his injury, and a discussion of his chances for complete recovery evidently aroused him, but never to the point at which a pilomotor response occurred in any part of the body. As will be seen, however, this does not affect the conclusions. Interruption of the intraspinal neurone obviously precludes the passage of any impulses from the higher centres to the lateral horn cells. Among his many examples of spinal cord lesions, André Thomas ((32), p. 154) includes one which demonstrates this point perfectly. The case is that of a woman, who at operation, was found to have a pachymeningitis at the eighth and ninth dorsal segments. Her lower extremities and abdominal wall

were paralyzed, and she had fecal incontinence and urgency with retardation of micturition. The patellar and ankle jerks were exaggerated and the Babinski reflex was present on both sides. There were marked sensory changes below the level of the lesion. The woman was subject to crises of pain, during which she frequently sweated on the arms and on the trunk down to the level of the umbilicus.

Reaction to Adrenalin

Subcutaneous injections of adrenalin were given in the left arm, in doses ranging from 0.3 to 0.7 cc. There was no evident response to any of them.

Sweating Phenomena

There was a marked spontaneous hyperhidrosis of the right axilla observed at each examination. Pilocarpine (0.01 gr.) was injected subcutaneously into the left arm. There was a slight general sweating, somewhat but not greatly exaggerated in the hyperreflexic zone on the trunk and arm.

Summary and Conclusions Regarding the Case of Partial Spinal Cord Section

The fibers innervating the skin of the trunk up to the shoulder, and of the arm and fore-arm, leave the cord below the level of the fourth dorsal segment; the hyperreflexic zone must be supplied by fibers emerging from the cord below the level of the lesion, which was at the fourth dorsal segment. This fact was originally deduced by André Thomas from a considerable number of cases; and is illustrated in his map ((32), end of Chap. III). Fay also gives some interesting examples of interruption of the pilomotor reflex arc in spinal cord lesions (12).

The hyperreflexia is much more evident down to and through the twelfth dorsal segment than below that level, just as are the instances of what might be called the emotional pilomotor reaction in the hemiplegias. The author has no good explanation to advance for this fact. It seems worth while, however, to call attention to the possible relationship of this phenomenon to Winkler's observation (28), mentioned above, that the stimulation of the frontoventral part of the frontal lobe produced sweating which was most pronounced in the forepart of the body.

Here, then, is another instance of an inhibitory function in a neurone belonging to the sympathetic nervous system. The peripheral neurone was overactive, both spontaneously and when made to take part in a reflex action. The section of the neurone running down to the lateral horn cell must have involved the loss of an inhibitory influence, exactly as in the case of a pyramidal tract lesion.

GENERAL COMMENT

The Multiplicity of Sympathetic Neurones within the Nervous System

The excessive pilomotor activity in the two cases of hemiplegia did not include any hyperreflexia, but was manifested only after central (emotional) stimulation. This fact distinguishes the implicated neurone from the one concerned in the case of partial spinal cord interruption. Consequently, there must be at least two sympathetic neurones within the central nervous system. One of them evidently originates somewhere in the cortex (neurone I) and the other terminates around the cell giving origin to the peripheral axone (neurone II; see Fig. 129). The point of juncture cannot be definitely established at the present moment, but the evidence points to the hypothalamus, the caudoventral and perhaps the medial portions of the thalamus, as the loci where the synapse probably takes place. The experiments of Winkler (33), of Karplus and Kreidl (17–22), of Woodworth and Sherrington (34), of Cannon and Britton (8), and of Bard (1), all suggest this conclusion. It is, of course, also possible that some such synapses may occur, additionally, in a variety of places.

It is still necessary to show that the effects in the hemiplegia cases depend definitely upon the capsular lesion, and not upon the involvement of pericapsular structures, such as the corpus striatum or parts of the diencephalon. The question at once focuses itself upon the latter regions, because the evidence implicating the corpus striatum as a part of the sympathetic nervous system is very dubious. The very fact that some diencephalic parts are certainly major sympathetic nuclei, suggests almost beyond a doubt that they are the cells which give rise to the axones of neurone II, or at least to the majority of them. A lesion of these cells, then, should give the same effect as an interruption of the axones of neurone II, of which the pilomotor behavior in spinal cord injuries is an example. But the pilomotor

consequences in the hemiplegia patients contrast so sharply with those in spinal cord cases that, as has been seen, the effects cannot be due to

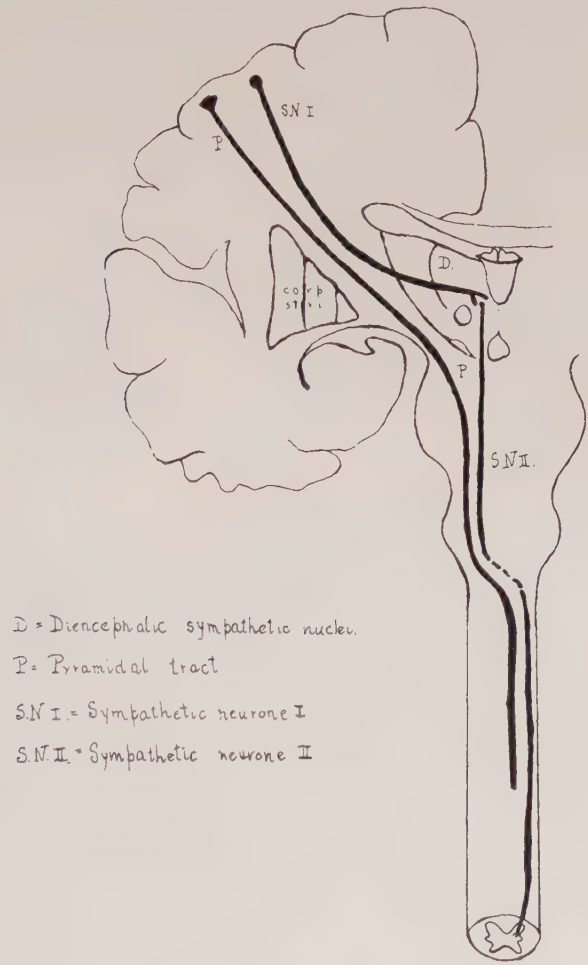


FIG. 129. Diagram showing the probable relations of sympathetic neurones I and II to each other, to the pyramidal tract and to the rest of the nervous system, according to the evidence about them which has so far been evolved.

a lesion anywhere in neurone II. They must, therefore, result from a disturbance in a part higher than the diencephalic nuclei, and

the causal lesion can be no other than the one in the internal capsule. Moreover, the injury in the two hemiplegias was evidently small; there were no alterations in sensibility, nor was there the slightest somatic suggestion of any disorder in the pericapsular structures.

Position of the Sympathetic Tracts in the Central Nervous System

The sympathetic fibers probably run in company with the pyramidal ones, at least in the internal capsule. The claim was made by Charcot (9) and by Nothnagel (28) that the vasomotor fibers run in the posterior limb of the capsule, probably between the motor and sensory contingents. The lesions causing the hemiplegias here reported, were probably well localized, since there were no somatic disturbances except those of the motor system; and the fact that the sympathetic fibers were included, points strongly to their close proximity to the pyramidal axones. This is probably also true in the cord; if the two tracts are closely associated in one part of the nervous system, the likelihood is great that the relationship is constant. Moreover, in all cases of column spinal cord injury (most of which have been reported by André Thomas; see especially his monograph (32)) in which the pilomotor reflex is exaggerated below the level of the lesion, the pyramidal tract is also injured; the author knows of none without somatic motor disturbance in which there is pilomotor hyperreflexia. It is certain that the sympathetic pathway is a crossed one, at least in part, since the destruction of neurone I produces heterolateral, and of neurone II, homolateral disturbances.

Relationship of Spasticity to Increased Pilomotor Activity

From the two hemiplegia cases, it seems reasonable to conclude that there is no relationship between spasticity and increased pilomotor activity. One patient, H. B., was extremely spastic, in both arm and leg; the other had only a trace of spasticity,—yet the pilomotor manifestations were the same in both.

The Relationship of the Inhibition Shown in the Sympathetic System to That in the Other Parts of the Nervous System

The first actual recognition of the release phenomenon in the sympathetic nervous system seems to be that recently made by Bard (1), in his comprehensive paper on its behavior after cortical ablation. He saw, in the sham rage phenomenon, a loss of inhibition over the

primary sympathetic centres. It cannot be assumed that the inhibitory function revealed in the sympathetic part of the nervous system differs, in any fundamental manner, from that exhibited in other parts.

The excess motor activity following the destruction of pyramidal fibers, is too well known to require treatment here. The inhibition in the sensory system was first stressed by Head and Holmes (15), who suggested convincingly that the severe spontaneous pains in some instances of thalamic disturbance were due to interruption of fibers from the cortex which act upon and control the sensory centres in the thalamus. This, they said, is an example of loss of cortical inhibition, with resultant release and overplay of the fundamental functions of the sensory part of the thalamus. The sympathetic is the only system about which much is known, that contains two descending neurones within the central nervous system. For this reason, it lends itself peculiarly to a study of certain phases of the function of inhibition.

The separate destruction of neurones I and II provides two distinct examples of inhibition in the same system. If neurone I is interrupted, neurone II overacts when excited; if neurone II is destroyed, there is an excess of activity by the peripheral neurone, when stimulated. Thus, the sympathetic neurones give a clear and definitive illustration of the principle that if a descending neurone is interrupted, the neurone below it, upon which it plays, will overact when stimulated.

The actual nature of the inhibitory power is, of course, far from being comprehended. An understanding of it may eventually be gained through a complete knowledge of its various properties. Through their arrangement, sympathetic neurones I and II indicate very clearly some of those properties.

The ability of any neurone to inhibit, must be part of the inherent function of that particular neurone, independent of the activities of neurones situated higher up. Thus, the inhibitory function of neurone II continues to manifest itself in a normal manner, regardless of whether or not neurone I is intact. This is shown by the fact that if neurone I is interrupted, as in the two hemiplegia cases, the sympathetic reflex arc goes on functioning normally,—there is no increase in the pilomotor response which is provoked reflexly by stimulation of the skin.

By the same fact, it is shown that the inhibitory power is not of such a nature as to be transmissible from one neurone to another.

This becomes obvious as soon as it is appreciated that the loss of inhibitory power by neurone I is not transmitted to neurone II.

The behavior of neurone II makes it certain that the release phenomenon is not merely a matter of release. In other words, the loss of control by the inhibitory neurone is not, in itself, a sufficient stimulus to cause overactivity of the lower neurone. There must also be excitement of that lower neurone. This must be true because it would not have been known—probably this is the reason, in fact, for its having escaped recognition—that the interruption of neurone I had resulted in the loss of inhibition of neurone II, had not neurone II been stimulated by arousing an emotion. No spontaneous goose-flesh was ever noted in either of the two hemiplegia patients; actual excitement of neurone II was always essential to the demonstration of the loss of the inhibitory faculty of the interrupted neurone I. It seems reasonable to generalize from this fact, and to draw the conclusion that in all the instances of definite nervous inhibition which are reasonably well known, the manifestations of hyperactivity are due not only to a loss of the control of a higher neurone, but to the stimulation of the still active neurone, as well. Such instances include the lower motor neurone after pyramidal tract injury, the pain phenomena in many cases of thalamic destruction, and the exaggerated simple pilomotor reflex after interruption of neurone II. It may be objected that, if this is true of the pain following thalamic lesions, there should also be spontaneous pain after the destruction of the spinothalamic tract, whenever ordinarily painful stimuli are applied to the skin. Such a result is, of course, impossible, because pain cannot be perceived if the spinothalamic tract is interrupted.

The Possible Rôle of the Cortical Neurone in Certain Mental Disturbances

The present paper is not the place for a discussion of this subject. It may be mentioned, however, that changes in the function of the cortical neurone may play a part in the production of the sympathetic disturbances wherever they occur in the so-called mental disorders. Vasomotor, sudoral, cardiac, gastric, intestinal and genital aberrations are common in the hysterias, in anxiety, and in other neuroses.

SUMMARY

1. Two patients with hemiplegia are described in whom any emotional experience produces exaggerated pilomotor phenomena on the hemiplegic side. The simple pilomotor reflex in the same zone is normal. The behavior of the pilomotor system in these two cases is contrasted with that in a patient with partial section of the spinal cord, in which, while the simple reflex is exaggerated, there are no abnormal phenomena in response to an emotional stimulus.

2. The human cortex is the site of origin of a neurone which exercises a definite influence over, and is a part of, the sympathetic nervous system. This neurone (I) probably terminates in the hypothalamus and in parts of the thalamus, whence the second (II) descends to the intraspinal cells of the first peripheral sympathetic neurone. In the hemiplegia cases there is interruption of neurone I; and in the spinal cord case, of neurone II.

3. Neurone I passes through the internal capsule. Neurone II probably decussates in company with the pyramidal fibers; and presumably continues this association with the pyramidal system, in the cord.

4. The release phenomenon is a general principle, and applies to the sympathetic as well as to the other parts of the nervous system. When neurone I is interrupted, hyperfunction of neurone II is exhibited upon stimulation; the destruction of neurone II causes an exaggeration of the activity of the peripheral sympathetic neurones.

5. Because of their arrangement, the sympathetic tracts are suitable for a study of certain properties of the phenomenon of inhibition, a fact which leads to the following conclusions:

(*a*) The ability of any neurone to inhibit, is an inherent part of the function of that particular neurone, independent of the activities of neurones situated higher up.

(*b*) The inhibitory power is not of such a nature as to be transmissible from one neurone to another.

(*c*) The release phenomenon is not merely a matter of the release of the lower neurone from higher control; the lower neurone must itself undergo stimulation, if there is to be a demonstration that a loss of inhibition has occurred. The loss of control of a higher neurone over a lower is not, in itself, sufficient stimulus to cause the overactivity of the latter. The lower neurone must also be specifically stimulated in order to become hyperactive.

DISCUSSION

The following questions submitted to Dr. Brickner before the Commission, together with the answers to them, are here reported verbatim.

Dr. Spiller: Is it not possible, Dr. Brickner, that the cortical neurone is not in the internal capsule but is in the extrapyramidal system, and that this increased reaction through the sympathetic nervous system is the result of the loss of the inhibition which is exerted through the pyramidal tract over the sympathetic system. There is close interrelation between the corpus striatum and the capsular fibers. There is evidence that the basal ganglia are a part of the sympathetic system.

Krafft-Ebing (23) many years ago called attention to the fact that the tendon-reflexes are usually exaggerated in true Parkinson's disease, the existence of which we must still acknowledge notwithstanding the evidence of the epidemic encephalitic form. This exaggeration may come through the pyramidal tract better than in any other way, even though we accept Parkinson's disease as the result of lesions in the basal ganglia.

Dr. Brickner: I considered that, Dr. Spiller, and I do not believe that that is the case, for the following reason: As I said, we have evidence that the so-called central sympathetic centres are located in the thalamus and possibly, though not very probably according to the evidence, in the corpus striatum.

If that is the case, what I called neurone II, must arise in that area; but in the hemiplegic cases the sympathetic phenomena are totally different from those observed when neurone II is injured. Therefore, the lesion cannot involve neurone II and must involve another neurone which I presume must be in the capsule and not in these sympathetic nuclei.

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CHAPTER XXVI

A STUDY OF THE SWEATING REACTION INDUCED BY THE ADMINISTRATION OF PILOCARPINE IN DISEASES OF THE SPINAL CORD[1]

An Aid in Localizing the Segmental Level of Spinal Cord Neoplasms

C. BURNS CRAIG, M.D.

INTRODUCTION

SIR VICTOR HORSLEY (4) stated that in the majority of spinal cord compression cases the injection of 0.25 gr. of pilocarpine would produce a sharp contrast between the normal and the paralytic areas, the line of junction being marked by a line of drops of sweat. The present paper describes an investigation undertaken to determine whether such a reaction could be of value in the localizing of spinal cord tumors.

Langley (5) has pointed out that Horsley's observation involves two factors: first, the covering of the patient so abundantly and warming him to such a degree that natural sweating is produced; and second, the use of pilocarpine to augment the reaction already excited. The first reaction is of central and the second, of peripheral origin. Pharmacologists agree that the action of pilocarpine is peripheral, that it is probably on the terminal neural mechanism or the cell-membrane of the secreting cell (2, 7, 8).

The question then arises as to how a lesion in the spinal cord can affect the secreting cell when the postganglionic neurone is intact. J. H. Burn (1), in discussing Horsley's statement, concludes that the interference in cord-compression must be in the first factor, the initiation of central sweating. The peripheral action of pilocarpine only accentuates the active area above the spinal cord lesion in contrast with the paralytic area below the cord lesion. Burn compares the

[1] The cases reported are from the Neurological Institute, New York. The operations were performed either by Dr. Charles A. Elsberg, Dr. A. S. Taylor, or Dr. Byron Stookey.

patient having a spinal lesion with a kitten in which the sciatic nerve has been severed. When the patient is thoroughly warmed and then given pilocarpine, the sweating is more profuse in the area above the lesion. If the kitten with the severed nerve, is placed in a room at 37°C. and then given pilocarpine, sweating occurs earlier and more profusely on the normal paw. From his experiments Burn concludes that the degeneration of the sympathetic nerve-supply to the cat's foot is not followed by a diminution in the sweating reaction to pilocarpine; that the section of the mixed nerve-supply to an extremity (degeneration having taken place) causes an immediate exaggeration followed by a great diminution of the sweating evoked by pilocarpine. He suggests that the diminished sweating response is due to defective capillary tone. The sweating response to pilocarpine, depressed after complete denervation, can be temporarily restored by the injection of adrenalin. Burn (1) agrees with Langley and Anderson ((6), p. 423) that pilocarpine may cause sweating after the destruction of the nerve-supply, but that denervation affects the pilocarpine response; since degeneration of the mixed nerve-supply leads to diminution of the sweat-secretion, and degeneration of the sympathetic fibers allows an increase in sweat-secretion. It seems possible, therefore, that the destruction of neurones in the spinal cord or interference with their function by compression might cause an interference with the sweating mechanism comparable to an interference with the sensory function.

In the following cases the sweating reaction has been compared with the pain perception because where there is sensory disorder due to a spinal lesion, the most precise level of the pathology is revealed by an alteration in the sense of pain.

It is a fault of graphic representations, such as charts, that they make the findings and interpretations appear more exact than they actually were. Nevertheless the following figures represent the results of the present investigation as accurately as possible with this method of portrayal.

The following procedure was employed: After the patient had been in bed for one hour, pilocarpine solution was injected under the skin of the left arm, two or three hours after the last meal. Ordinarily the patient was covered with a sheet and two blankets, the second blanket being thrown over him just before the injection of the drug.

CASE REPORTS

B6911DH. History. A boy twelve years old complained of inability to walk, and of incontinence of urine and feces. Four years previous to admission he had begun to trip over slight unevennesses and soon became clumsy in walking. Seven months after the clumsiness had started, he noticed stiffness in attempting to stand. His knees would give way under him and he would fall forward. About the same time he lost control of the bladder and rectal sphincters. He never complained of pain or of unusual sensations. The stiffness in his lower extremities had been progressive and the patient on admission was unable to stand or walk.

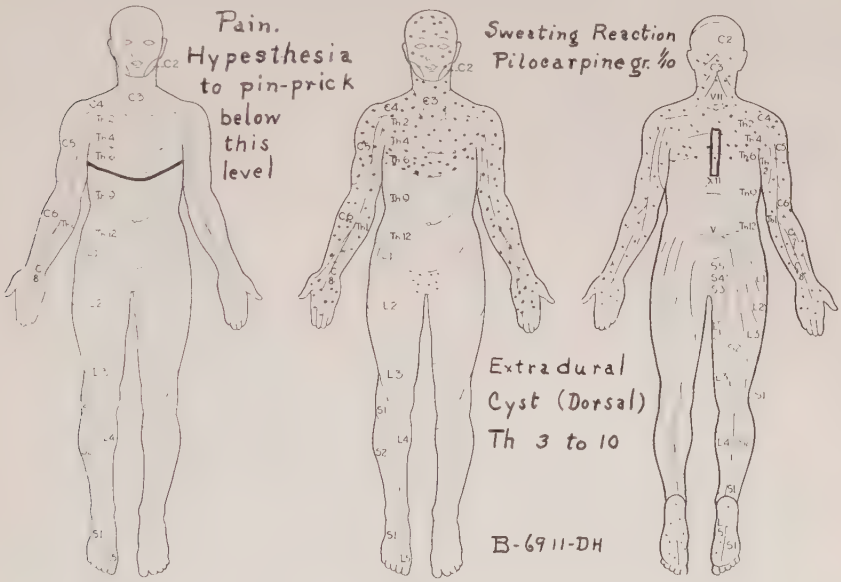

FIG. 130

Examination. The lower extremities were in a highly spastic condition, with the thighs, legs, and feet flexed so that when supported he rested on the balls of his feet in a half-squatting posture. There was no atrophy. The reflexes harmonized with the spastic state,—all were increased in the lower extremities and a Babinski reflex was present on both sides.

The cranial nerves and the upper extremities were negative.

The patient was generally obese and there was a lumbar scoliosis. Sensory examination showed a diminution to touch, pain, and temperature below the sixth rib. The vibratory sense was absent in the lower extremities and pelvis.

The manometer showed a block in the spinal fluid of the lumbar region. The spinal fluid showed 3 cells per cmm., 1 plus globulin, negative colloidal gold, 80 mg. of protein, and the Wassermann in both spinal fluid and blood was negative.

Blood count and urine were negative. The X-ray showed slight left scoliosis in the lumbar region and in the upper thoracic region, with compensatory twisting. The sacro-iliac joints were widely separated and rather poorly developed. After the injection of lipiodol in the lumbar region, the X-ray showed that some of this substance had reached the cervical region although it had not passed freely through the midthoracic region.

Course. On November 3, 1927, 0.1 gr. of pilocarpine was given. In eight minutes sweating appeared upon the palms and soles; in ten minutes, upon the upper lip; in twelve minutes, upon the forehead; in fifteen minutes, upon the cheeks and neck; and in twenty minutes, covered the upper trunk to the ensiform process

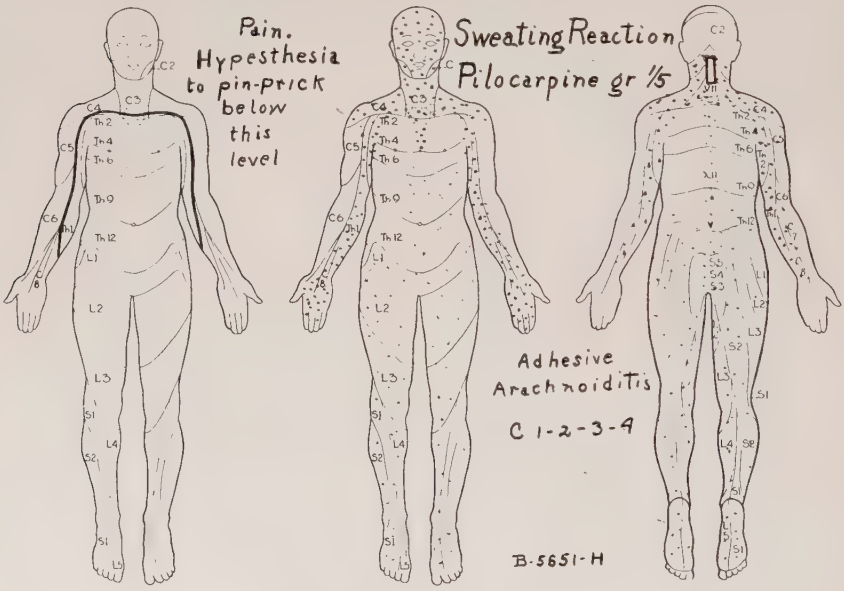

FIG. 131

anteriorly and the ninth thoracic spine posteriorly. Below this level the body was dry.

Operation. On November 4, 1927, a laminectomy of the fourth to the tenth thoracic vertebrae was performed. An extradural cyst of unknown origin, extending throughout the exposure, was found. (See Fig. 130.)

B5651H. History. A man thirty-three years old complained of difficulty in walking due to weakness in the legs, especially the right, associated with cramps in the legs. Five months prior to admission the patient had noticed coldness and numbness in the knees, which he thought was caused by the draughty place where he worked. Very soon the weakness in the legs developed. The coldness in the knees disappeared in about a month, the cramps grew more frequent, and weak-

ness in the lower extremities became so intense that he swayed as he walked. He had, at various times, pain in the lumbar region.

Examination. The patient was a well-nourished, well-developed man, with an unsteady, jerky, slightly spastic gait. He swayed in the Rombert position, with the eyes either open or closed. He was unsteady when on the right foot alone, but secure on the left. There was some dysmetria in both the right and left lower extremities and some weakness in flexion and extension of the lower extremities, though this was not marked. He was unable to sit up from the supine position. There was no atrophy. The upper extremities were negative. Reflexes were slightly increased in the upper extremities, of average activity in the left lower extremity, and increased in the right lower extremity. All superficial reflexes were absent. Babinski's sign was present on both sides.

The sensory examination showed a diminution to pain below the first rib anteriorly and the seventh cervical spinous process posteriorly, and on the inner aspects of both arms down to the middle of the fore-arms. The temperature sensation was diminished, as follows: cold below the second rib, hot below the waist. Touch was diminished below the sixth rib. Vibration was absent up to the third lumbar vertebra.

The cranial nerves were negative except that the right visual field showed a paracentral scotoma which was thought to be congenital. The limits of the fields and discs were normal.

The manometer at the time of the lumbar puncture showed on one occasion a doubtful block and at another time what was interpreted as a complete block. The spinal fluid was clear, containing 93 cells per cmm., 1 plus globulin, and 50 mg. of protein. The Wassermann was negative. The urine and blood were normal. The X-ray of the spine was negative.

Course. On November 28, 1927, the patient was given 0.2 gr. of pilocarpine. In four minutes sweating appeared about the neck and in the axillae. In six minutes, upon the upper lip and forehead. In thirteen minutes the patient was sweating generally. Sweating was profuse over the face, neck, above the clavicle, across the tips of the shoulders, down the inner aspect of both arms, and on the palms, extending also a little way down the sternum. The remainder of the trunk, the outer surface of the arm, and the lower extremities were only moist.

Operation. On November 29, 1927, a left hemilaminectomy including the first four cervical vertebrae was performed. The arachnoid was found adherent to the dorsal surface of the spinal cord throughout the exposure. (See Fig. 131.)

B8011H. History. A man thirty-five years old complained of stiffness and weakness in both legs, and difficulty in walking. About ten years prior to admission the patient had noticed an occasional biting sensation in the right knee and leg and a feeling of coldness in the sole of the right foot. This was usually followed by a pain in the right leg. The right foot was disposed to sweat a great deal. There was a slow, steady progression in his inability to use his lower extremities dexterously. About three years before admission they became so stiff and heavy that he did most of his work sitting down. On walking a block he would have to stop and rest two or three times. He arose one morning as usual and went to market. On returning home he helped to unload a truck. He felt unusually tired, and sat down. When he tried to rise he found he could not. He was lifted and carried

to bed. Both legs were stiff and crossed in spasm. He was in bed about six weeks. At the end of that time he was able to sit up, and by holding on to the furniture he could walk across the room. Within a week he walked with the aid of crutches and later, of canes. About six months before admission the patient began to have difficulty in starting or stopping the stream of urine. During the ten years of the progress of the disease, all difficulties were confined to the lower extremities and bladder. There was no disorder of speech nor trouble with the upper extremities. There were no remissions.

Examination. The patient was a well-nourished, well-developed man, exhibiting a markedly spastic gait with decided adductor spasm. He was unable to stand except with support, and walked with a cane. The reflexes in the lower extremities

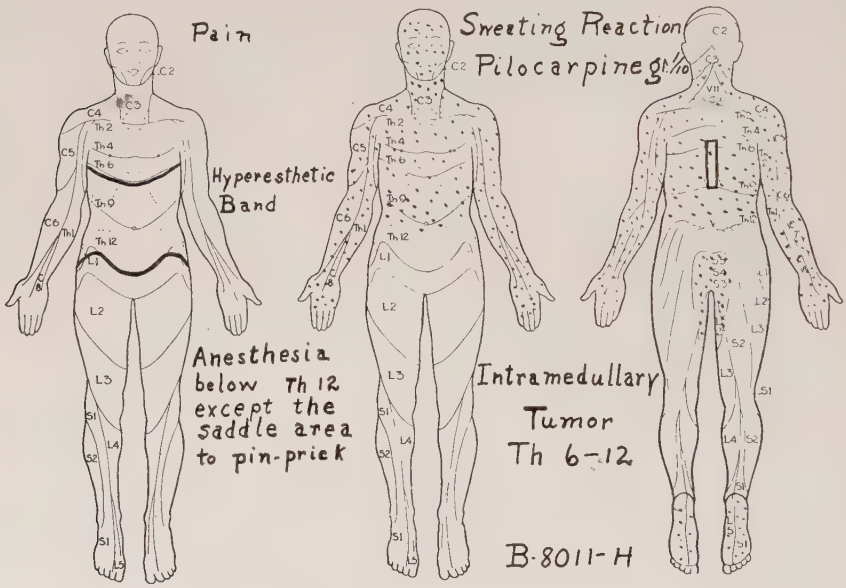

FIG. 132

were greatly exaggerated. There were bilateral ankle-clonus and Babinski signs. The existence of the superficial abdominal reflexes was doubtful. The upper extremities were negative. The adductor spasm in the lower extremities prevented abduction. There was no atrophy. Co-ordination tests in the upper extremities were negative. It was not possible to test the lower extremities because of the extreme spasticity.

The sensory examination revealed a diminution to touch, pain and temperature below the top of the pubic bone anteriorly and the top of the sacrum posteriorly, except in the saddle area. Above this was a broad band of increased sensibility. The vibratory sense was lost in the toes and ankles and diminished throughout the lower extremities and the pelvis up to the fifth lumbar vertebra.

The cranial nerves were negative, except for a few nystagmoid jerks laterally to the right and left,—and upward.

The manometric reading of the spinal fluid indicated an incomplete blocking of the flow to the lumbar region. The spinal fluid showed no cells, 1 plus globulin, negative colloidal gold, 50 mg. protein. The Wassermann in the spinal fluid and blood was negative. The blood count and urine were negative. The X-ray of the spine was negative.

Course. On December 1, 1927, the patient was given 0.1 gr. of pilocarpine. In seven minutes sweating appeared upon the upper lip and forehead, and rapidly spread to the neck and trunk. The thorax and arms were quite moist. Around

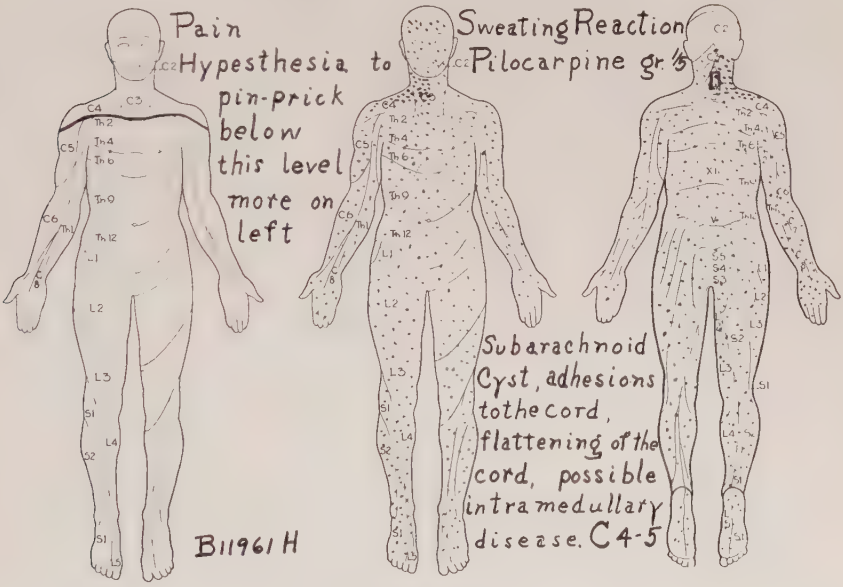

Fig. 133

the waist sweating was profuse. Below the top of the sacrum and the lower abdominal region the skin remained dry except for the soles of the feet and the inner surfaces of the thighs.

Operation. On December 12, 1927, a right hemilaminectomy from the seventh to the eleventh thoracic vertebrae inclusive was performed. There were diffuse adhesions of the arachnoid to the spinal cord, and an ovoid intramedullary tumor 3 x 2 x 2 cm. was found at the level of the eleventh and twelfth thoracic segments. (See Fig. 132.)

B11961H. History. A woman forty-seven years old complained of numbness, tingling, and iciness in both hands, a weakness in the right arm and leg, pain in the right side of the neck. These symptoms had begun about four years previous

to admission, with tingling, numbness, and coldness in the fingertips of both hands, which progressed and involved both hands up to the wrists. This persisted up to the time of her admission to the hospital, without remission. For about the same period there had been an awkwardness in the finer movements of the fingers, which become more marked about six months before admission. At that time a definite weakness began in the right hand, gradually involving the fore-arm and then the arm. Three months later she noticed that the muscles of the right shoulder, arm, and fore-arm were smaller than those on the left. She then noticed that she could not distinguish hot and cold objects well with her hands, and less well with the left than with the right. From the onset of her illness, the patient experienced an intermittent soreness in the back of the head and a stiffness of the right side of the neck. For about eight months she had noticed a tendency to drag the right foot, which grew steadily worse, until at the time of admission she walked with some difficulty. There was a sense of tightness, numbness, and coldness in the form of a band around the lower chest. The bowels became constipated and a frequency of urination developed.

Examination. The patient was a small, poorly-developed woman who dragged her right foot in walking and showed the loss of associated movement of her right arm. Her sense of station was fairly secure, but when she closed her eyes, a backward swaying developed. She could stand on the left foot, but not on the right. There was a slight dysmetria in the finger-nose test, more marked on the right side. Other tests of co-ordination showed an impairment in the right upper extremity. Co-ordination tests of the right lower extremity showed a similar impairment. The strength was impaired in the right upper extremity. There was some atrophy of the muscles of the right shoulder girdle. The deep reflexes were increased in all the extremities, more on the right side than on the left. There was no clonus, no Babinski sign. Hoffman's sign was present on the right. The superficial reflexes were not obtained.

The sensory examination showed that the sense of touch, pain, and temperature was diminished below the clavicle anteriorly and the seventh cervical spinous process posteriorly. The vibratory sense was diminished from the toes to the knee, and seemed to be lost in the pelvis, ribs, and spine up to the second thoracic vertebra. On the right it was also lost in the ulnar fingers and the arm up to the shoulder. On the left it was impaired from the wrist to the elbow, and was absent from the elbow to the shoulder. There was no disorder in the muscle-tendon sense. Cranial nerves were negative.

The manometric test for blocking in the spinal fluid was negative. The spinal fluid was clear, with no cells, nor excessive globulin. The Wassermann in the spinal fluid and blood was negative. The urine and blood count were negative. The X-ray of the spine was negative.

Course. The patient stated that she did not perspire much, even in hot weather. On May 27, 1928, 0.2 gr. of pilocarpine was given. In three minutes sweating appeared on the forehead, and a minute later on the lower and upper lips. Then the palms became moist. In six minutes lachrymation and salivation occurred, and a minute later the desire to urinate. Eleven minutes after the injection there was a profuse sweating on the neck, more marked on the right side. Within two minutes thereafter the patient was moist all over. The sweating was the most

profuse over the face and neck, particularly on the right side of the neck, and extended down over the sternum. From the clavicle down, the skin was moist but there was less sweating than above the clavicle. Posteriorly the sweating was more marked on the right than on the left side of the trunk.

Operation. On May 28, 1928, a laminectomy of the second to the fifth and part of the first cervical vertebrae was performed. Adhesions of the arachnoid to the right side of the cord were disclosed, together with an arachnoidal cyst at the level of the fourth cervical segment on the right side, with flattening of the spinal cord. The surface of the exposed cord was flattened and covered with numerous fine vessels indicating an inflammatory lesion. (See Fig. 133.)

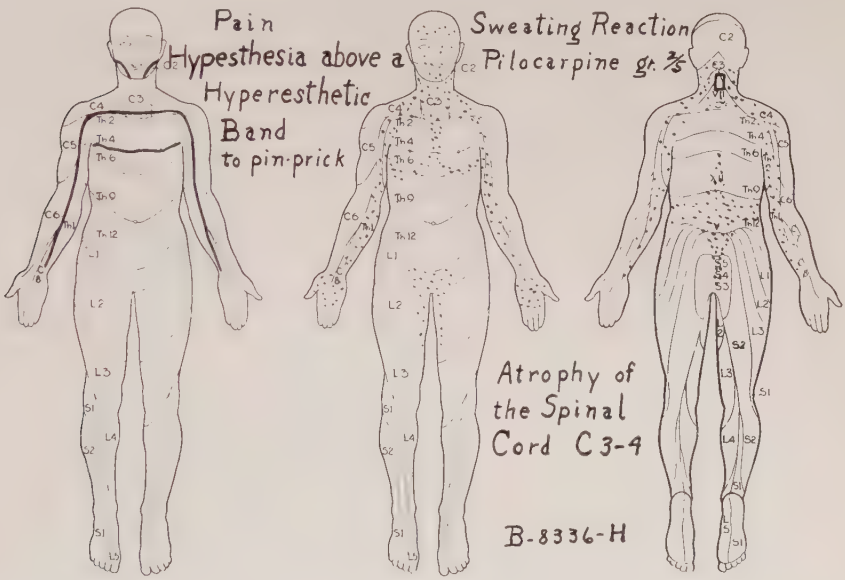

FIG. 134

B8336H. History. A woman forty-two years old had trouble in walking and in using her arms. Seven years previously the patient had suffered from attacks of pain in both arms, diagnosed as neuritis. During these attacks she could scarcely use her arms and when the pain was severe she could not even feed herself. After two years the severe pain wore off leaving the arms with a tired feeling. Since that time she had been unable to distinguish the texture of cloth with the tips of her fingers. Her arms had never been well since, and she had had trouble in doing her housework. About three years previous to admission she began to have difficulty in the use of her legs. They became numb and weak, and the feet heavy to lift. The only pain was an occasional cramp in the soles. There was frequent involuntary jumping in the legs while in bed. As the weakness and heaviness in the legs progressed, the ability to walk diminished. About a year previously, the weak-

ness in the lower extremities became so marked that she was scarcely able to walk at all. The arms also became weaker. There had been no improvement up to the time of admission.

Examination. The patient was a slender woman who walked unsteadily with a spastic gait. Equilibration tests were poorly done. There was marked dysmetria in the left upper extremity. The tendon-reflexes were increased in both the upper and lower extremities. The superficial reflexes were absent. Hoffman's sign and a bilateral Babinski sign were present. There was a diminution in strength in the left hand and arm, in both legs, and in the flexion of the feet. She was unable to lift the left leg from the bed. The cranial nerves were negative, as was the visceral examination. There was a marked kyphosis in the thoracic

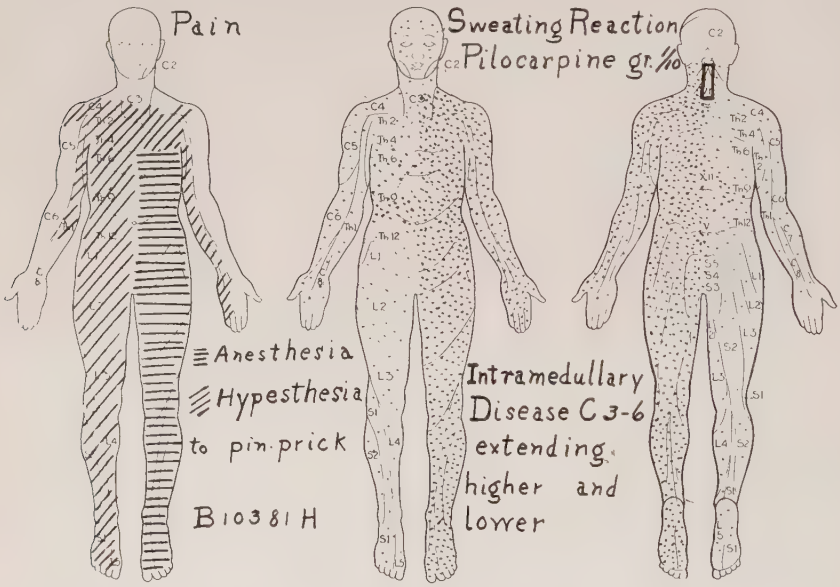

Fig. 135

region. The sensory examination showed a hyperesthetic band from the first to the fifth rib anteriorly and from the first to the sixth thoracic spine posteriorly. Above this band sensation was diminished up to the distribution of the trifacial nerve. This finding was manifest more particularly to pinprick and temperature. It was also present to a lesser degree to cotton wool. There was no disorder of the muscle-tendon sense; but there was a slight decrease in the vibratory sense in the legs.

The manometric reading of the spinal fluid showed a slowing of the fall in pressure on compression but this was not sufficient, however, to be a definite block. The spinal fluid was negative throughout,—no cells, no globulin, no colloidal gold curve, protein 24 mg. The Wassermann in the spinal fluid and blood was negative. The blood chemistry was normal. The blood count and urine were normal.

Course. On December 20, 1927, 0.4 gr. of pilocarpine was given. (This large dose was administered, because 0.2 gr. produced no effect.) The patient stated that she never sweated in summer nor in a hot bath. Lachrymation occurred in three minutes. Sweating began in four minutes in the axillae, on the palms, ulnar side of the fore-arms, neck and forehead. Salivation appeared. The chest, front and back, became moist and beads of sweat stood out in the lumbar region and up and down the spine. The pubic area and inner surface of the thighs were moist. One hour and fifteen minutes after the injection the patient was shivering all over. There were fascicular twitchings in the fore-arms, quadriceps, and pectorals.

Operation. On January 12, 1928, a left hemilaminectomy of the cervical vertebrae from the first to the sixth inclusive was performed. The spinal cord was found to be atrophic in the second and third segments. Delicate adhesions of the arachnoid were present. (See Fig. 134.)

B10381H. History. A woman forty-eight years of age complained of difficulty in the use of the legs, and pain in the legs and left arm. The disease began two years before admission, with weakness in the left leg and inability to hurry in walking. Then both legs became stiff, so that she had to rub them on getting out of bed in the morning before attempting to walk. These symptoms disappeared during the warm weather, but recurred the following winter, accompanied by intermittent pain in the legs and left arm. The weakness and stiffness in the lower extremities progressed so that a year previous to admission she had become unable to walk without support. She became chronically constipated, and began to have difficulty in urinating. For some months prior to admission the patient complained of numbness and "pins and needles" in her feet, and also of a tight band sensation around her calves or thighs at times. For one month the intermittent pain in the legs and left arm had been increasing. For six months the patient had noted a tendency to increased sweating involving the entire body, more marked when in bed.

Examination. The patient was a large, powerfully-built woman, who lay in bed and was unable to arise therefrom, or to walk. There was a marked weakness in both lower extremities, more pronounced on the left side. The flexor muscles were weaker than the extensor muscles. Flexion and extension of the left foot were absent. She could not raise the left leg from the bed. There was a marked hypertonicity of all the muscles of the lower extremities, but no atrophy. There were occasional mass involuntary movements in the legs. No disorder of co-ordination and no loss of strength appeared in the upper extremities. The reflexes were increased moderately in the upper extremities and very considerably in the lower extremities. Ankle-clonus and Babinski's sign were present on both sides. Superficial abdominal reflexes were absent. The cranial nerves were negative. There was erythema of the hands and fore-arms and cyanosis of the feet. The hands, arms, legs, and feet were blotchy and slightly edematous. Pigmented spots were present over the abdomen. There was a marked sweating over the entire body. This profuse sweating would last for several hours at a time. The thyroid gland was palpable.

The sensory examination showed anesthesia to touch and pain over the left lower extremity, and the left half of the trunk up to the fifth rib anteriorly and to the middle of the scapula posteriorly. Hypesthesia to touch and pain existed over

the right lower extremity, the right half of the trunk up to the base of the neck anteriorly and posteriorly, and on the inner aspects of both arms. The temperature sense was diminished and confused on both sides of the body up to the clavicle anteriorly and to the seventh cervical spine posteriorly. The sense of vibration was lost up to the twelfth thoracic spine, and diminished in the lower ribs and in both arms. The muscle-joint sense was lost in the ankles, knees and hips.

The manometer reading and lumbar puncture indicated a complete block in the spinal fluid circulation. The spinal fluid was very yellow, the globulin excess was 4 plus, and the protein 400 mg. There were no cells. The colloidal gold test was negative. The Wassermann in the spinal fluid and blood was negative. The

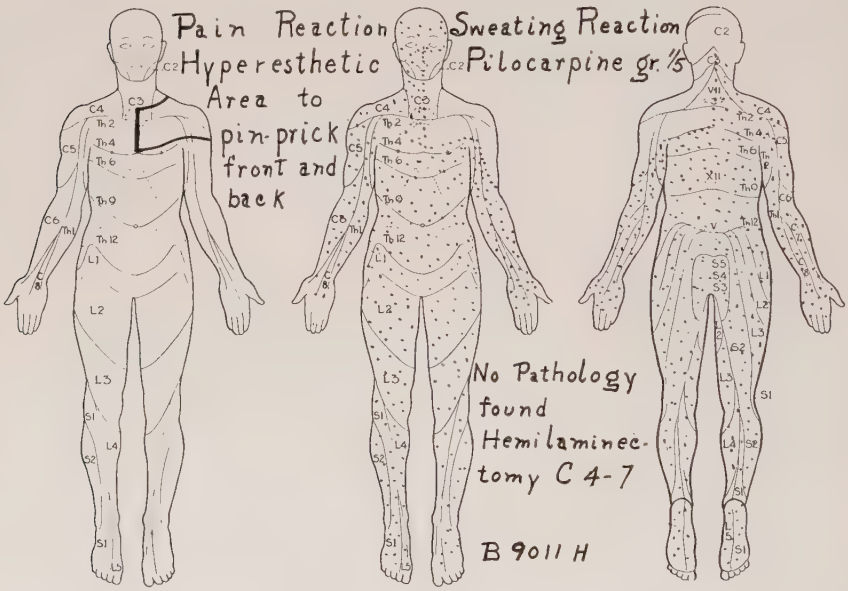

Fig. 136

blood count and urine were normal. The X-ray of the spine showed a slight scoliosis in the upper thoracic region, otherwise the picture was negative.

Course. On March 18, 1928, 0.1 gr. of pilocarpine was given. Profuse sweating followed in six minutes. It involved the entire left half of the body up to the base of the neck, and spread across the right side of the abdomen and the right lumbar region. Generally the right half of the body was moist, whereas the left half of the body was bathed in excessive sweat. Salivation and urgent urination occurred in six minutes. The forehead was moist, the rest of the face almost dry, and the neck slightly moist.

This patient was in an almost constant state of sweating, which the pilocarpine accentuated, producing a greater response on the left side of the body. This rela-

tively more profuse sweating on the side which showed the greater sensory paralysis was contrary to the result in the other cases. But in this case the sweating mechanism was differently deranged, as was indicated by the frequent periods of spontaneous sweating.

Operation. On March 21, 1928, laminectomy of the third to the sixth cervical vertebrae was performed. Intramedullary disease extending throughout the exposed area and continuing higher and lower, was found. (See Fig. 135.)

B9011H. History. A man forty-two years of age complained of excessively severe stabs of pain in the left shoulder and arm, and also of weakness in the left arm. His illness had begun a little over three years before the date of admission, with slight twinges of pain in the left shoulder, which would last from ten minutes to two hours but which might not recur for three or four days. Six or eight months after the onset, the pain became more severe and would radiate to the lower border of the left scapula and the left side of the chest, and to the inner surface of the left arm to the elbow. The pain was continuous. It would last throughout the day and into the night. He would get up and sit in a rocking-chair at night, in order to gain some relief. He received no relief from medication. Raising the arm, as when holding a strap while riding in the subway, augmented the pain. Lying on the right side caused the pain in the left arm to become worse, but lying on the left side caused the pain in the inner surface of the left arm to become still more acute. On awakening he frequently experienced a throbbing, pulling pain in the left scapular region, which tended to draw his neck toward the left. About four months before admission, while walking he frequently experienced a suffocating sensation in the epigastrium, which would force him to stop and stand perfectly still until it had passed. This disappeared after a week.

Examination. The patient was a poorly-developed and poorly-nourished man who exhibited a tendency to hold his head tilted toward the left. There was no disorder of gait, equilibration, or co-ordination. There was marked tremor of the fingers with the arms extended. The tendon reflexes were all present and slightly greater in the right upper and lower extremities than in the left ones. No pathological reflexes existed. The superficial reflexes were present. There was a slight weakness in the muscles of the left side of the neck, and in the left biceps and triceps. The left scapular was more prominent than the right, due to a slight atrophy of the supra- and infraspinatus. There was also atrophy of the rhomboids, the muscles of the left side of the neck, the left biceps and triceps, and the flexor muscles of the left fore-arm, but no atrophy of the deltoid.

The sensory examination showed an irregular area of hyperesthesia to pain over the left shoulder and adjacent area of the trunk, anteriorly and posteriorly. The cranial nerves were negative. Repeated examination of the chest for intrathoracic or mediastinal disease failed to reveal the presence of such a condition. The X-ray showed an increased density in the superior mediastinum, more marked on the left side, and extending from the second to the third thoracic vertebra. There was no compression of the trachea. The density was not definitely shaped, as would have been likely in a circumscribed new growth. It suggested a mediastinitis due to infection.

The manometric reading for lumbar puncture showed no blocking. The spinal fluid showed no cells, no globulin, negative colloidal gold, 35 mg. protein, and a

negative Wassermann. The blood count and blood chemistry were normal. The urine was normal and negative for Bence-Jones bodies.

Course. On February 3, 1928, the patient was given 0.2 gr. of pilocarpine. In eight minutes sweating appeared on the forehead, on the palms, and in the axillae. Salivation occurred. At the end of thirteen minutes the sweating was general and profuse, involving the entire trunk, face, and extremities, except the left cheek, left side of the neck, left part of the chest down to the third interspace anteriorly and the mid-scapular region posteriorly, and the shoulder and the outer surface of the arm almost to the elbow. This area remained dry.

Operation. On February 4, 1928, a left hemilaminectomy of the fourth to the seventh cervical vertebrae inclusive was performed. No pathological condition was found.

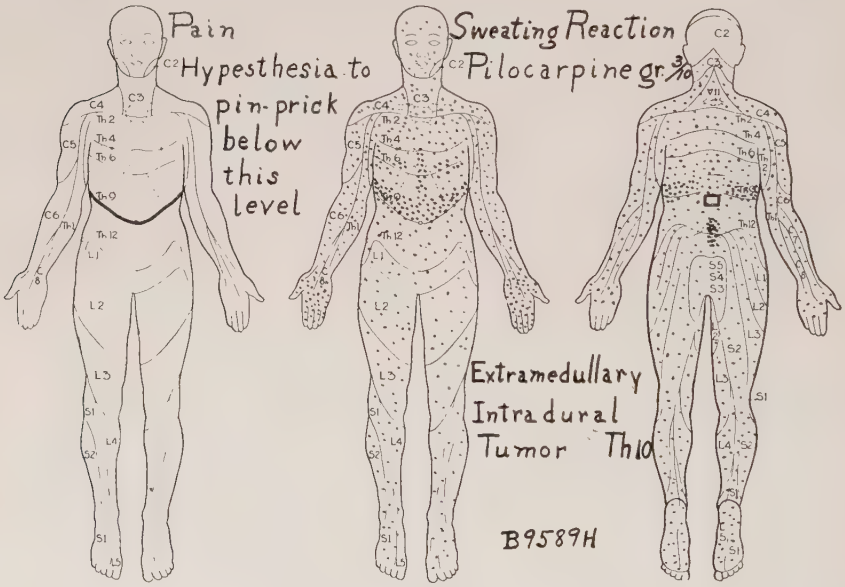

Fig. 137

Any interpretation of the results was impossible. If the increased density in the superior mediastinum was due to mediastinitis, the inflammatory process might have involved the rami communicantes or thoracic ganglia of the sympathetic chain. (See Fig. 136.)

B9589H. History. A woman twenty-one years of age complained of pain low down on the left side of the back, numbness, weakness, tingling in both legs, and difficulty in walking. The first symptom of illness was the pain in the left lumbar region, which had begun about a year previous to admission. Three months later she experienced sensations of tingling and numbness in the right leg associated with weakness. After three more months the left leg displayed the same symptoms.

The weakness and difficulty in the use of her legs progressed slowly during the succeeding six months, at the end of which time she was admitted to the hospital.

Examination. The examination showed a stocky young Italian woman, who walked about somewhat stiffly, exhibiting a slight drag in both legs and swinging the feet outward with each step in order to get the toes off the floor. The sense of equilibration was very good with the eyes open. With the eyes closed, there was marked swaying. The patient was very insecure in standing on either foot alone. Tests in co-ordination were well carried out by the upper extremities, but only fairly well done by the lower extremities. The reflexes were increased in the lower extremities. There was a doubtful Babinski sign on each side. The lower abdominal reflexes were absent. The reflexes in the upper extremities were negative. There was some diminution in strength in the lower extremities, which was more pronounced on the left side. There was no atrophy. The cranial nerves were all negative. The visceral examination was negative. The sensory examination showed a diminution to touch, pain, and temperature below the umbilicus anteriorly and the twelfth thoracic spinous process posteriorly. The sense of vibration was lost up to the fifth lumbar vertebra. There was disorder of the position sense throughout the lower extremities, particularly in the toes.

The manometer indicated a block in the spinal fluid circulation. The spinal fluid was of a uniform slightly yellowish color, the globulin excess was 4 plus, the protein 400 mg., the cells 2 per cmm., the colloidal gold negative, the Wassermann negative in the blood and spinal fluid, the blood count normal and the urine negative. The X-ray examination showed an increased density of bone in the fourth and fifth thoracic vertebrae, suggestive of early osteitis, otherwise the picture was negative.

Course. The patient stated that she perspired readily in warm weather. On February 14, 1928, 0.1 gr. of pilocarpine was given, without result. On February 15, 0.2 gr. of pilocarpine was given, still without result. On February 17, 0.3 gr. of pilocarpine was administered. Within two minutes the face became flushed and salivation occurred. In six minutes sweat appeared on the forehead, upper lip, and in the palms and axillae. In sixteen minutes there was urgency of urination and pain in the bladder. In twenty-one minutes there was present a band of beads of sweat two inches wide extending around the waist just above the umbilicus. Beads of sweat also appeared over the median line anteriorly from the level of the fifth rib to the umbilicus and beneath the breasts. Sweating on the palms was profuse. Beads appeared over the fifth lumbar and first sacral vertebra. The sweating spread upwards from the waist; and the cheeks, neck, and arms became moist. Below the waist the trunk and lower extremities became moist, but distinctly less so than the upper part of the body.

This is the only case which in any way corroborated Horsley's observation that a line of drops of sweat would separate the normal and paralytic areas. Over the dermatomere immediately above the one corresponding to the segmental site of the spinal cord compression, the sweat appeared as a band of beads extending around the trunk, and the sweating above the segment of the lesion was more marked than that below it.

Operation. On February 18, 1928, a laminectomy of the sixth to the ninth thoracic vertebrae was performed. A fibrous tumor 3 x 1.5 x 1.5 cm., arising from

the inner surface of the dura and lying left dorsolaterally at the tenth thoracic segment, was found. The spinal cord was markedly compressed and indented by the tumor. (See Fig. 137.)

CONCLUSIONS

From the foregoing series of cases the following conclusions are justified.

1. The sweating mechanism, stimulated by pilocarpine, may be disordered by lesions of the spinal cord.

2. The sweating reaction to pilocarpine is more seriously disturbed by tumors than by diffuse lesions, such as the changes in the spinal cord associated with adhesions of the arachnoid following subacute meningitis.

3. This test does not serve to differentiate extramedullary from intramedullary tumors of the spinal cord.

4. It is neither as accurate nor as dependable in determining the segmental level of spinal cord lesions as is the sensory examination.

DISCUSSION

The following questions submitted to Dr. Craig before the Commission, together with the answers to them, are here reported verbatim.

Dr. Temple Fay: Mr. President, two years ago, before the American Neurological Society, I presented thirteen verified cases of vasomotor and pilomotor manifestations from Dr. Spiller's service at the University Hospital (3). Since then we have had twenty-three verified cases, in which we have determined the upper level of the lesion by two factors; the vasomotor and the pilomotor responses. The sweating response has varied, and we have been led to conclude that it is not as reliable as the Thomas test for producing a pilomotor response. The Thomas test is determined by pressing or pinching in the region of the trapezius of the neck, producing a homolateral pilomotor response. In those cases where a sensory level was obtained, and where a spinal block existed, we failed to get the pilomotor responses below the level of the lesion in many cases, by a manometric reading. We inferred that the fibers within the cord carrying this response to lower levels had been interfered with. It gave us a good test for determining the upper level of the cord involvement indicated by the pilomotor response.

The root level was determined by the zone of hyperalgesia. This corresponds accurately with the vasomotor response, and we were able in one case to photograph this skin manifestation, with subsequent verification of the level of localization at operation.

I believe the vasomotor sign and hyperalgesia to be more important than any other factor that we may consider. The vasomotor response and hyperalgesia represent the upper level of root involvement.

I should like to ask a question as to the observations which Dr. Craig has made. Does he find that the root phenomena seem to be more important than the segmental phenomena? In other words, we have noted in one case after the removal of a tumor, in which two roots were cut at the time of operation, that the vasomotor level rose two segments to include the new root area destroyed. The sweating response failed to show in those two segments, although it had been present prior to the time of operation. The exact level of vasomotor response seems to correspond to the area of root irritation or compression, and is found to coincide with the zone of hyperalgesia when carefully tested by the comparative method.

We have observed in Dr. Spiller's service, on several occasions, the fact that the vasomotor flushing of the skin can be observed in a diffuse daylight striking the patient diagonally when viewed from the head or foot of the bed, without any other preparation than that the patient be warm, and placed in a suitable light. This level, irregular in shape and following somewhat the Henry Head zones for the dermatomeres, can be traced out accurately and will be found to correspond with the zone of hyperalgesia. From moment to moment sometimes, this zone of hyperemia fades, and with it the zone of hyperalgesia changes.

We have been led to feel (3) that perhaps the peripheral hyperalgesia which has been mentioned, is a response of the peripheral pain end-organs to the congestion of the skin-surface, due to the vasomotor hyperemia, and that this is caused by the irritated or compressed root in question, and not by the cord segment. Frequently, we have found the segmental cord sensory level of sensation lower than the root level. Thus localization by the vasomotor sign, hyperalgesia and pilomotor test has given a more accurate operative level, by indicating the highest root involved, and has proved far more satisfactory than the segmental level of disturbed sensation.

Dr. Craig: I do not believe I can answer Dr. Fay's question. I think it is a very interesting point, and he is probably correct. I shall have to follow it up.

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CHAPTER XXVII

DISTURBANCES IN THE VEGETATIVE SYSTEM IN DISEASES OF THE LUNGS AND VISCERAL PLEURA

FRANCIS M. POTTENGER, M.D.

I. Normal Activity in Vegetative Structures
   1. Tonus and Rhythm
II. Variability of Reflexes
III. Innervation of the Lungs and Visceral Pleura
IV. Innervation of the Parietal Pleura
V. Nature of the Many Reflexes Which May Arise from the Lung
VI. Somatic Reflexes of Pulmonary Origin
VII. Distribution of Pulmonary Sympathetic Reflexes in Somatic Structures
   1. Pulmonary Motor Reflex of Sympathetic Origin in Somatic Structures
   2. Pulmonary Sensory Reflex of Sympathetic Origin in Somatic Structures or in Referred Pain
   3. Pulmonary Trophic Reflex of Sympathetic Origin in Somatic Structures
VIII. Distribution of Pulmonary Parasympathetic Reflexes in Somatic Structures
   1. Pulmonary Motor Reflex of Parasympathetic Origin in Somatic Structures
   2. Pulmonary Sensory Reflex of Parasympathetic Origin in Somatic Structures
   3. Pulmonary Trophic Reflex of Parasympathetic Origin in Somatic Structures
IX. Reflexes of Pulmonary Origin Expressed in Other Viscera
   1. Viscero-Visceral Sympathetic Reflexes of Pulmonary Origin
      (*a*) Dilatation of the Pupil
      (*b*) Lessened Motility and Secretion in the Gastro-Intestinal Tract
      (*c*) Disturbances in Function of the Cardiac and Pyloric Sphincters
      (*d*) Tachycardia
   2. Viscero-Visceral Parasympathetic Reflexes of Pulmonary Origin
      (*a*) Larynx
      (*b*) Cough
      (*c*) Rhinopharyngeal Secretion
      (*d*) Flushing of the Face

(*e*) Bradycardia
(*f*) Increased Motility and Secretory Activity in the Gastro-Intestinal Tract. Spastic Colon, Diarrhea
3. Viscero-Trophic Reflexes
4. Sensory Reflexes
X. Relation of Toxic Symptoms to the Vegetative Nerves
XI. Parasympathetic Reflexes Expressed in the Lung Where the Stimulus Arises in Other Organs and Is Carried Centralwards over the Parasympathetic Nerves.

NORMAL ACTIVITY IN VEGETATIVE STRUCTURES

IN ORDER to discuss intelligently the manner in which changes in the vegetative system affect the thoracic viscera as well as the way in which diseases of the thoracic viscera affect the vegetative nerves and through them produce widespread effects in other tissues and organs, it is necessary to understand the nature of activity in the vegetative structure and the precise place in the scheme of activity which is occupied by the vegetative nerves. This is especially desirable now that vegetative neurology is being taken more into consideration in the explanation of pathological visceral phenomena.

Formerly, the part played by the nerves in producing activity in the vegetative structures was exaggerated. Too close an analogy was drawn between their part in the activation of the viscera and their part in the activation of the somatic structures. The severing of the nerve which supplies these structures is followed by a loss of function and by atrophy of the parts affected; and these results show that the nerve is necessary to function. It was but natural to assume a similar relationship between nerve and tissue in the vegetative structures until proven otherwise.

Much experimentation has helped to demonstrate that the real function of the nerves in visceral physiology is regulatory and integrative rather than primary and essential to activity. Experiments giving weight to this conclusion were performed by Goltz and Ewald (11), in which visceral function was found to continue after the removal of the cord; by Magnus (28–35), in which intestinal function was carried on after the plexus of Auerbach and Meissner had been totally removed; and by Cannon (5, 6), in which the heart and other organs continued to act after their complete denervation.

While the physiologists were working out the neurological side, biophysics came to the rescue with links in the chain of evidence

which clarified the situation. Ringer (61–63), in his work from 1880 to 1883, had already shown the importance of salts in tissue-activity, but the meaning of his observations was not comprehended until long afterwards. His results have now been confirmed, however, by many modern workers, such as Howell (14), Howell and Duke (15), Bayliss (1, 2), Zondek (67), Schade (64), Loewi (26), Lillie (22, 23), Kylin (17), Fischer (9), and Loeb (25). In fact, the importance and necessity of the salts to physiological action is now universally recognized. A review of the literature, particularly on calcium metabolism, has recently been given by Stewart and Percival (66).

Combining the conclusions of all these workers in biophysics, biochemistry, and neurophysiology, it is now possible to define tissue-activity in its physiological and pathological relationships in a way that gives it a clinical significance.

Tonus and Rhythm

The fact that the vegetative structures possess tonicity and rhythm, whether the nerve-connection is intact or severed, has definitely established the independence of outside influence as far as the mere ability to function is concerned. Cells are able to perform the acts necessary for the maintenance of their health and vigor for a considerable time in Ringer's solution or in Ringer-Locke solution, when they are separated from the body and its nerve- and hormone-influences.

The body-cells must now be considered as colloidal systems in a liquid state; and as representing different phases of solution of different degrees of cellular activity. When cells function they take on and give off electrolytes. Apparently the most important electrolytes, so far as their activity is concerned, are those of calcium, potassium and sodium. There are, however, others which are probably necessary to life and undoubtedly are necessary to adequate function, such as, phosphorus, magnesium and iron, which are present in smaller amounts; and probably still others, in infinitesimal amounts. This assumption is based upon a knowledge of plant physiology. Lipman (24) calls attention to the fact that one-quarter to one-half part of zinc or of boron per million parts of the solution in which plant-roots grow, will insure normal plant-life, while the absence of these substances prevents growth.

While function may be carried on without hormone- and nerve-influence, there can be no action commensurate with the requirements

of a complex organism, such as man, without the correlating and integrating operation of the chemical and nervous mechanisms. Nor must the vitamines be forgotten in this scheme of activity.

The vegetative nerves, then, while not essential to simple function, are necessary to the adequate and intelligent function of higher organisms, both in the relationship of the various parts and organs to each other and in the maintenance of the organism in a proper relationship to its environment. They have the very important and necessary function of aiding the organism in maintaining itself in a state of physiological balance. Hence they cause the various organs and tissues to act as a unit for the benefit of the organism as a whole. So important is this relationship that under certain conditions each afferent neurone may be connected for the purpose of mediating reflexes with every efferent neurone in the body.

VARIABILITY OF REFLEXES

In clinical practice the physician too often fails to take into consideration the individual factors influencing the patient's response to disease. Different constitutional organizations, different endocrine predominances, different nerve and psychical balances influence, in fact determine, the way in which man will react to a disease process. For in disease he is bound as a slave to the structural and functional peculiarities which dominated him in health. Preceding illness may have called upon his reserves and upon his equilibrium-producing mechanisms. They may even have lowered his margin of physiological safety to a point where certain activities will be thrown out of balance by stimuli which at a former time he could have resisted perfectly. Thus it makes a great difference to the sick individual how he was born; with what structural and functional characteristics he was endowed at birth; and how these structural endowments have been influenced by activities within and adjustments without.

INNERVATION OF THE LUNGS AND VISCERAL PLEURA

Since the vegetative nerves furnish the mechanism for the correlation and integration of normal visceral activities in states of health, they also furnish the mechanism for disseminating abnormal stimuli and bringing different structures of the body into pathological relationship under conditions of disease. In order to appreciate the full meaning of the vegetative nerves and their part in correlating patho-

logical stimuli, it is necessary to know the nerve-connection for each organ. Any unusual stimulation in an organ, such as that produced by disease, is accompanied by the possibility of being carried over

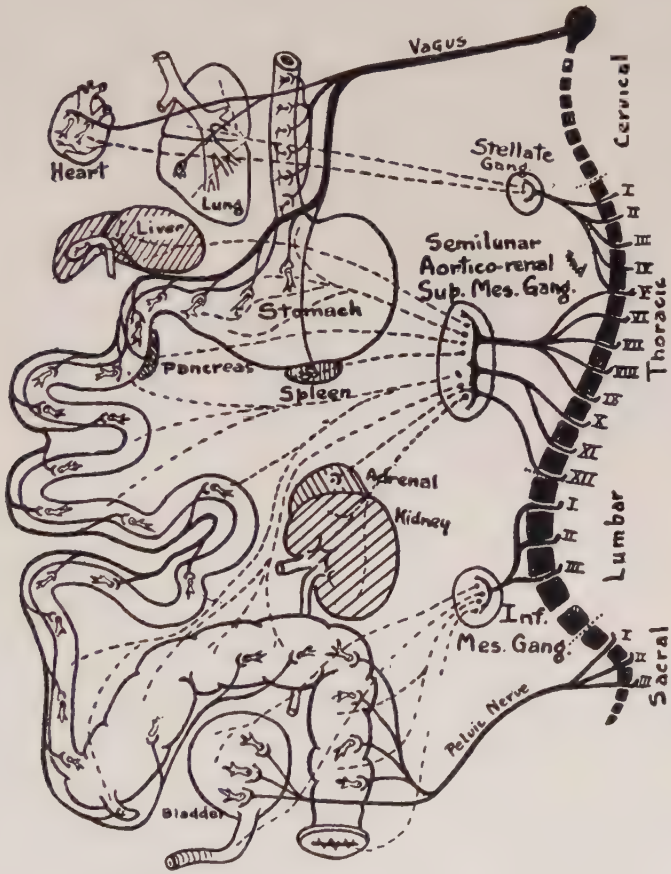

FIG. 138. Schematic illustration of the double innervation of the enteral system, showing the intimate relationship between the lung and the other important viscera.

The vagus and pelvic nerves (parasympathetic) are represented by solid black lines extending to the organ. The connector neurones of the sympathetic nerves are represented by solid black lines running to the ganglia. The postganglionic fibers running to the viscera are represented by dotted lines. The lung is innervated by both vagus (parasympathetic) and sympathetic fibers from the upper five thoracic segments. The sympathetic motor cells for the lung lie in the stellate ganglia. ((58), p. 219.)

connecting nerves to any or all of the organs which have a nerve-connection.

The innervation of the visceral pleura is the same as that of the lung;

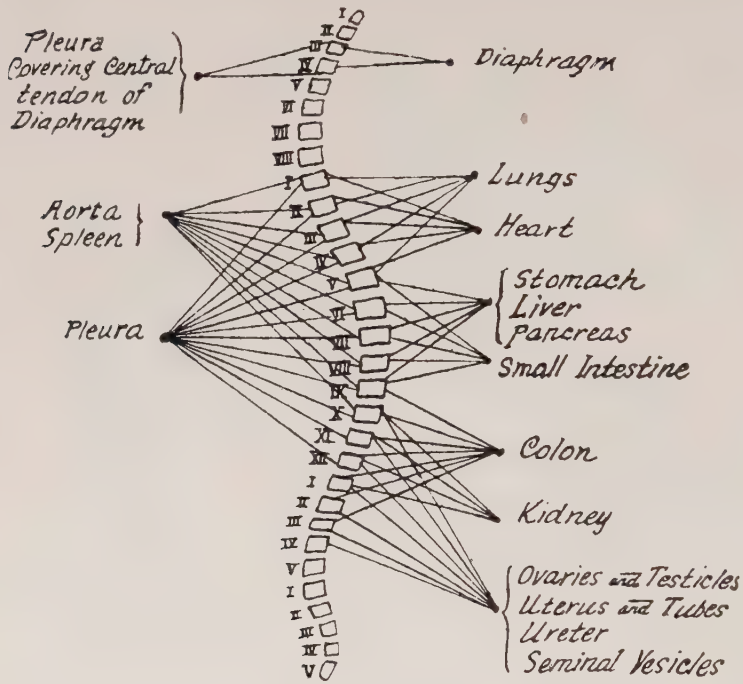

FIG. 139. The connector neurones for the important thoracic, abdominal and pelvic viscera.

In the figure the connecting neurones are those which belong to the thoraci-columbar outflow, except those going to the diaphragm, which are spinal nerves (phrenics). The motor cells for the viscera are found in the various collateral ganglia.

The figure shows that the innervation of the various viscera may be divided into groups. The heart and lungs are innervated from practically the same segments, the upper Ist to VIth thoracic; the stomach, liver, and pancreas from the same segments, Vth to IXth thoracic; and the colon, kidney, and pelvic viscera from practically the same segments, IXth and Xth thoracic to IIIrd and IVth lumbar; the visceral pleura, from the Ist to XIIth thoracic.

In spite of this grouping in innervation, each organ is brought into reflex connection with efferent neurones, both sensory and motor, which are more or less definite, in such a way that the motor and sensory reflexes do not overlap as much as might be indicated. ((58), p. 139.)

consequently both organs may be considered together. The lungs belong to the enteral system and have the same innervation (Gaskell (10)). This is shown in Fig. 138. These organs receive their activating fibers from the vagus and their inhibiting fibers from the sympathetic nerves. The bronchial musculature and the secreting glands of the bronchial mucosa are stimulated to activity when the pulmonary branches of the vagus nerve are activated; and their activity is inhibited when the pulmonary branches of the sympathetic system are stimulated.

That the effect of the vagus, when stimulated, is to contract the bronchi and trachea has been shown by the dilatation of these structures which follows the cutting of the vagi (Kahn (16)), and by the constriction which is again produced when the peripheral end of the cut nerve is stimulated (Einthoven (8)). The inhibiting, or dilator, effect of the sympathetic nerves has been shown by Dixon and Ransom (7), by stimulating the connector nerves which arise from thoracic segments I to III. It has been shown therapeutically by the relief of the bronchial spasm in asthma by the employment of adrenalin.

Not only are these structures innervated by nerves from both the sympathetic and parasympathetic systems, through which effects may be produced in the bronchial musculature and bronchial secretory glands; but what is of the greatest importance in the presence of visceral disease, the lungs and visceral pleura also possess afferent neurones belonging to both of these systems. When the bronchial musculature and mucous membrane, and the pleura are irritated these neurones pick up stimuli and carry them centralwards to join with spinal motor and sensory nerves in producing motor and trophic reflexes and sensory changes in skeletal structures, as well as reflex effects in other viscera. Many reflexes have their origin in the pulmonary tissue. Most of these are expressed in other tissues and organs. On the other hand, certain motor and secretory reflexes which are expressed in the bronchial musculature and glands, originate in other organs (Pottenger (44; 52; and 58, pp. 296–297)).

The blood-vessels of the lung receive innervation from thoracic segments III to VI, through the stellate ganglion (Bradford and Dean (3)); while the bronchial musculature and glands are innervated by thoracic segments I to V or VI (Fig. 139).

INNERVATION OF THE PARIETAL PLEURA

While the visceral pleura is innervated by the same neurones that supply the lung and therefore mediate somatic reflexes in the mid-cervical segments of the spinal cord, the parietal pleura, as well as the subpleural tissues, receive their innervation from the intercostal nerves of the somatic system. The latter carry with them sympa-

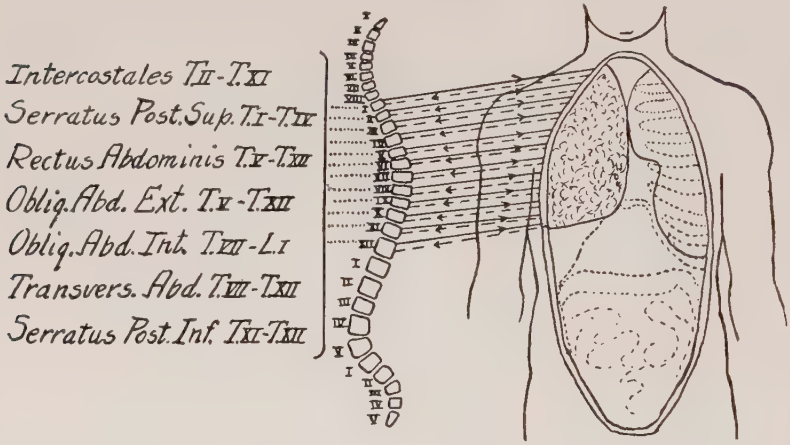

FIG. 140. Parietopleural viscero-motor reflex. The lines connecting the pleura with the segments of the cord from Ist to XIIth, represent both intercostal and sympathetic nerves. The solid lines represent the nerves supplying the pleura. The broken lines represent the sensory nerves which carry afferent impulses to the cord from the pleura. The dotted lines on the other side of the cord represent corresponding spinal nerves which receive the impulses from the sensory sympathetic nerves and transmit them to the muscles shown, producing the pleural viscero-motor reflex.

It will be seen that the abdominal muscles may also be involved in the parietopleural viscero-motor reflex; that at times, particularly when the lower portion of the pleura is involved, this shows as a marked spasm which is sometimes considered to indicate acute disease of the abdominal viscera. ((58), p. 299.)

thetic fibers, as is shown in Figure 139. Both of these must be considered as being sources of reflex action (Pottenger (49; and 58, pp. 298–300)).

That the parietal pleura is innervated by intercostal nerves of the somatic system explains the fact of its being one of the viscera which, on irritation, may show pain of an acute character such as is not to be found in the viscera innervated wholly by vegetative neurones.

The difference in segmental connection between the parietal and visceral pleura is born out by the clinical manifestations of the somatic reflexes. Motor and trophic reflexes, as well as pain from the parietal pleura, are expressed through the intercostal nerves. These nerves have a wide distribution and one that is quite different from that arising from the visceral pleura. The intercostal muscles, the serratus posticus, superior and inferior, the rectus abdominis, and the obliquus externus and internus, may all show spasm (Fig. 140). The same muscles, as well as the skin and subcutaneous tissue innervated by the thoracic segments, show the trophic reflex, which is usually confined to more restricted areas than those reached by the reflexes from the visceral pleura and lung Sensory disturbance and the trophic reflex are regularly shown in the sensory thoracic nerves; but are limited in extent to the area covering the chronically inflamed pleura.

While pain and the trophic reflex are most regularly shown immediately over the seat of inflammation, they may extend downwards over the abdomen (45, 49, 50). Parietal pleural reflexes, motor, sensory and trophic, may all extend downwards over the abdomen at times, and become a source of much confusion in diagnosis. When pain and reflex muscle-spasm, caused by stimuli originating in the lower costal and costodiaphragmatic pleura, extend downwards, as they occasionally do, they simulate pain and the motor reflex which are due to the inflammation of the abdominal viscera (49). Their path is evident because the lower six intercostal nerves supply the lower segments of the pleura and also furnish sensation and motor activity for the abdominal skeletal structures.

NATURE OF THE MANY REFLEXES WHICH MAY ARISE FROM THE LUNG

When lung-tissue is the seat of an inflammatory process, such as that caused by pulmonary tuberculosis, it may express this condition through reflex effects in the somatic structures with which it is connected by afferent sympathetic and parasympathetic neurones, as well as by efferent somatic neurones. This inflammatory process may be manifested in three different ways: (*a*) it may produce spasm in the muscles; (*b*) it may, if the process becomes chronic, cause atrophy of the skin, subcutaneous tissue and muscles; or (*c*) it may give rise to pain and other sensory phenomena. The location of the reflex phenomena from impulses transmitted over the sympathetic and parasympathetic neurones, differs, as will appear in the subsequent discussion.

TABLE VI

Pulmonary Reflexes in Skeletal Structures in Which Afferent Stimuli Course Centralwards over the Sympathetic Nerves; and Efferent, over the Cervical Spinal Nerves, Principally CIII, CIV and CV

I. Motor reflexes when the disease is active, as follows:
   1. Spastic contraction of the muscles of the shoulder girdle (sternocleidomastoideus, scaleni, pectorales, subclavius, trapezius, levator anguli scapulae, rhomboidei) and the crus and central tendon of the diaphragm.
   2. Limited motion of the half of the thorax on which the diseased lung is found, through reflex spastic contraction of the sternocleidomastoideus, scaleni and subclavius above, and the crus and central tendon of the diaphragm below.

II. Trophic reflexes when the disease becomes chronic, or has healed, as follows:
   1. Atrophy of the muscles of the shoulder girdle.
   2. Atrophy of the skin between the second rib and angle of the jaw anteriorly; and the spine of the scapula and the base of the skull posteriorly.
   3. Atrophy of the subcutaneous tissue in the areas mentioned in No. 2.

III. Sensory reflexes, as follows:
   1. Altered sensation, both superficial and deep, usually in the form of discomfort or aching rather than sharp pain; noted both when the disease is acute and when chronic.
   2. Vasomotor phenomena producing flushing of the ear through the third cervical sensory nerve, when the disease is active.

TABLE VII

Pulmonary Reflexes in Skeletal Structures in Which Afferent Stimuli Course Centralwards over the Parasympathetic Nerves (Vagi); and Efferent, over the Various Cranial Nerves

I. Motor reflexes when the disease is active, as follows:
   1. Spasm of the sternocleidomastoideus and trapezius, through the spinal accessory. (Possibly spasm of all muscles of the shoulder girdle, through cervical nerves, as suggested by Rasmussen (59, 60).)
   2. Probable motor reflexes in the facial muscles through the facialis and trigeminus, since these atrophy when the process becomes chronic.

II. Trophic reflexes when the disease becomes chronic or has healed, as follows:
   1. In the facial muscles, through the facialis and trigeminus.

III. Sensory reflexes, as follows:
   1. Headache, face-ache, through the sensory branches of the trigeminus, both when the disease is acute and when chronic.
   2. Vasomotor phenomena producing flushing of the face, through the sensory fibers of the trigeminus, when the disease is active.

In the visceral structures with which the lungs are connected by afferent and efferent nerves belonging to the sympathetic and parasympathetic systems, pulmonary inflammation may also be expressed reflexly in at least two, and probably in three ways: (*a*) by an increase or inhibition of muscular activity; and (*b*) by an increase or inhibition of secretory activity; and probably (*c*) by the production of trophic changes. Tables VI to IX show the more common pulmonary reflexes as observed clinically, together with the paths over which their stimuli are carried ((58), p. 275).

TABLE VIII

VISCERO-VISCERAL PULMONARY REFLEXES IN WHICH BOTH AFFERENT AND EFFERENT STIMULI COURSE OVER THE SYMPATHETIC NERVES

I. Motor and secretory visceral reflexes when the disease is active, such as:
   1. Dilatation of pupil.
   2. Inhibition of motor and secretory activity in the gastro-intestinal canal.
   3. Spasm of sphincters in the gastro-intestinal canal.
   4. Increased heart-action (tachycardia).
   5. Probable decreased motility and decreased secretory activity in the ducts and glands of the gall-bladder, liver and pancreas, although not readily proven.

II. Probable trophic reflexes in structures subject to reflex action, when the disease is chronic or has healed.

SOMATIC REFLEXES OF PULMONARY ORIGIN

In the author's early description of the reflexes from impulses arising in the lung, he fell into some error because their pathways had not yet been worked out by the physiologists. His first announcement of the spasm of the skeletal muscles, as observed in clinical tuberculosis, was to the effect that "inflammation of the lung and pleura produced a spasm of the muscles of the chest wall, particularly of the intercostals" (37-39). At that time he was not able to differentiate between the reflexes arising in the pleura and those originating in the lung. He also failed to differentiate the increased resistance noted over the infiltrated area, from the increased tension of the muscles. Hence this increased resistance was ascribed to the newly discovered spasm of the muscles. It was only after much observation and study that it was possible to demonstrate the existence of two distinct sets of reflexes, since the innervation of the lung and visceral pleura differed from that of the

parietal pleura. In the author's later writings (55, 57), he made it quite clear that the somatic reflexes from the lung are mediated in the midcervical segments of the cord; and those from the parietal pleura, in thoracic segments I to XII (50).

TABLE IX

VISCERO-VISCERAL PULMONARY REFLEXES IN WHICH BOTH AFFERENT AND EFFERENT STIMULI COURSE OVER THE PARASYMPATHETIC NERVES

I. Motor and secretory visceral reflexes when the disease is active, such as:
   1. Increased secretion in the mucous glands of the nasal and nasopharyngeal mucous membranes (catarrh) through the VIIth cranial nerve.
   2. Disturbances in the motility of the vocal cords through the superior and inferior laryngeal nerves.
   3. Probable motor reflexes in the lingual muscles through the hypoglossus, since this atrophies when the disease becomes chronic.
   4. Slowing of heart through the vagus.
   5. Increased motility and increased secretory activity in gastro-intestinal canal through the gastric and intestinal fibers of the vagus, favoring appetite and digestion.
   6. Probable increased motility and increased secretory activity in the ducts and glands of liver, gall-bladder and pancreas, favoring digestion, although not readily proven.
   7. Cough, the afferent impulse being carried over the vagus to a centre from which efferent impulses go out, producing action in the abductor muscles of the larynx over the inferior laryngeal nerve, and in all expiratory muscles through the various spinal nerves; and simultaneously producing inhibition of action in the abductor muscles of the larynx and the muscles of inspiration.

II. Trophic reflexes in structures subject to reflex action when the disease is chronic or has healed:
   1. In the tongue, causing atrophy and deviation toward affected side, through the hypoglossus and lingual.
   2. In the tissues of the nasopharynx through the facialis.
   3. In the larynx, through superior and inferior laryngeal nerves.
   4. Probably in heart, gastro-intestinal tract, liver and pancreas, though not readily proven.

III. Sensory phenomena:
   1. Laryngeal irritation through the superior laryngeal nerve.

The somatic and visceral structures have definite segmental relationships. These structures and the organs embryologically belonging to the same cord segments, are prone to be most closely bound in reflex action. Therefore, a knowledge of the segments of the cord

to which given viscera are embryologically related, permits the assumption of knowledge as to the structures most apt to be influenced reflexly when they become the seat of inflammation. This fact is evident, since excessive stimuli from any organ, are carried centralwards and transferred, usually in the same segment which receives them, to other neurones for expression, according to certain physiologic laws (53).

According to Sherrington's law (65), "each afferent root finds in the immediate proximity to its own place of entrance in the cord, that is in the same segment, a reflex motor path of as low a threshold and as high a potency as is open to it elsewhere." This statement furnishes the key to all the viscero-somatic reflexes, whether of sympathetic or parasympathetic origin, and applies to all the important viscera, with the probable exception of the lung. The pulmonary somatic reflexes whose afferent stimuli course over the sympathetic neurones, apparently deviate from the rule in that the impulses enter the upper thoracic segments, but express reflex effects in the midcervical spinal nerves. Therefore, the impulses must be relayed upwards into the cervical segments of the cord by intercalated neurones, if the reflex is of sympathetic origin. The fact that the lung in embryo arises from the gut far forwards in the region of the pharynx, furnishes the anatomical and physiological basis for this relationship.

The reflexes from the lung express themselves most strongly in the midcervical segments of the cord whence arises the phrenic nerve which supplies the diaphragm. The diaphragm and lung, as they move caudad in development, still preserve their cervical connection in the cord, a fact which probably determines the midcervical location of the pulmonary reflexes. In order to apply Sherrington's law to the lung, the author has suggested the following modification, ((58), p. 152): "Impulses arising from a given viscus are transferred centralward to those segments of the cord with which that particular viscus is related embryologically; and, each afferent impulse finds in that particular segment to which it is finally transferred a reflex motor path of as low a threshold and of as high potency as any open to it anywhere."

The fact that impulses from the lung may course over afferent vagus fibers too, and cause spasm in the sternocleidomastoideus and trapezius, led Rasmussen (59, 60) to suggest the possibility of a central connection of the vagus with the midcervical spinal nerves as a cause of the motor reflex found in other muscles of the shoulder girdle and the

diaphragm. His suggestion is based upon the work of Larsell (18–21), and particularly upon the fact that Larsell found that most of the afferent fibers from the lung course in the vagus. The reflex path is quite clear between the vagus and the spinal accessory nerve in the production of spasm of the sternocleidomastoideus and trapezius. But since these muscles also receive part of their innervation from the spinal nerves arising in the midcervical segments; and, since other muscles receiving innervation from these segments, notably the scaleni, levator anguli scapulae, rhomboidei, crus and central tendon of the diaphragm also show the motor reflex from the lung; and, particularly, since the central cells of the accessorius are so intimately associated with cells of the spinal nerves, Rasmussen suggests that the pulmonary motor reflexes in all the muscles of the shoulder girdle which the present author first observed clinically, and which he has described as being of sympathetic origin, are probably at least partly produced by impulses which course over the vagus.

In support of the theory that the lung reflexes in the midcervical segments are at least mostly of sympathetic rather than of vagal origin, the author desires to point out the following facts which seem pertinent (51):

1. The lung and diaphragm are embryologically related to the midcervical segments of the spinal cord, just as the heart is related to the upper thoracic segments; and the stomach, liver, pancreas and small intestine, to the midthoracic segments.

2. It is known that the more important thoracic, abdominal and pelvic viscera, with the exception of the lung, produce motor and sensory, and (under conditions of long continued action) trophic reflexes in the somatic structures. These structures are innervated by the spinal nerves whose cell-bodies lie in those particular segments of the cord entered by the afferent sympathetic fibers, coming from the viscus in question, in accordance with Sherrington's law.

3. The lung is an exception to this law in that the upper thoracic spinal nerves do not mediate pulmonary reflexes in the tissues supplied by them, although the afferent sympathetic fibers enter these segments. This fact indicates that the segmental paths which are open to afferent sympathetic impulses in all other important viscera, according to Sherrington's law, are not open to the sympathetic impulses arising in the lung.

4. Other viscera are related embryologically to the segments in

which their sympathetic motor, trophic and sensory reflexes are mediated. Hence it seems reasonable to assume that the same embryological relationship is maintained in the case of the lung and that the impulses arising in the lung are transmitted through intersegmental paths, to the midcervical segments before the reflexes are mediated.

5. It is reasonable to assume that those pulmonary reflexes which are expressed in the somatic structures innervated by the midcervical nerves, are either of sympathetic origin; or that there are no pulmonary reflexes of sympathetic origin in somatic structures.

6. If these midcervical reflexes are of parasympathetic origin, they should be found regularly in other organs innervated by the vagus; but this is not the case.

It cannot be denied that reflexes in the somatic structures innervated by the midcervical portion of the cord may occur through impulses carried by both sympathetic and vagus afferent fibers; yet, the evidence in favor of their sympathetic origin appears to be stronger, except in the case of the sternocleidomastoideus and trapezius, which are known to have a double reflex connection. Analogy with the other viscera also supports this contention.

DISTRIBUTION OF PULMONARY SYMPATHETIC REFLEXES IN SOMATIC STRUCTURES

It may be assumed that the following somatic phenomena produced by afferent impulses from an inflamed lung are of sympathetic origin ((58), p. 272).

1. A motor reflex in those muscles which receive innervation from the midcervical segments of the cord.
2. Trophic changes in those areas of the skin, the subcutaneous tissues and the muscles which receive innervation from the midcervical segments of the cord.
3. Sensory changes in the tissues which receive innervation from the midcervical segments

Pulmonary Motor Reflex of Sympathetic Origin in Somatic Structures

The motor reflex is found in muscles receiving innervation particularly from the third, fourth and fifth cervical segments, Figure 141. Under conditions of excessive stimulation, it may spread to higher or lower levels and involve other muscles, according to the physiological law governing the spread of reflexes (53).

The muscles of importance in showing the pulmonary reflex, together with their innervation, are as follows:

Sternocleidomastoideus, C2 and spinal accessory
Scaleni muscles, C3 to C8
Subclavius, C5
Pectoralis major and minor, C5, C6 and C7
Trapezius, C2, C3 and C4 and spinal accessory
Levator anguli scapulae, C5, also C4
Rhomboidei, C5, also C4
Diaphragm, crus and central tendon, C4, also C3 and C5

It is at once evident that the muscles of this particular group have very important functions to perform with reference to respiration. The diaphragm is the most important of these muscles in this group which comprises all of the important accessory muscles of respiration. Whenever a lung is the seat of inflammation, the muscles on the affected side are thrown into reflex spasm. The effects are best shown in tuberculosis because the inflammation is of such a nature as to involve many nerve-endings. In this way they fix the chest wall. A shortening of the crus of the diaphragm below and of the scaleni, subclavius and sternocleidomastoideus above, acts as a splint on the affected side and lessens motion, thus putting the side at rest. This condition furnishes two valuable diagnostic signs of active pulmonary inflammation: (*a*) increased tension of the muscles of the shoulder girdle; and (*b*) limited motion of the side.

Pulmonary Sensory Reflex of Sympathetic Origin in Somatic Structures or in Referred Pain

Head (12) was the first to study pulmonary pain systematically, and to associate it with its corresponding skeletal zones. Since a motor effector is a *sine qua non* for a true reflex, there can be no such thing physiologically as a sensory reflex. It may, however, be recognized, as a clinical convenience. Furthermore, there is a transference of impulse in the central cell stations although it occurs in a different manner from that of the true reflex.

Because the viscero-sensory reflex is not a true reflex in the physiological sense, and because it is expressed in the somatic sensory nerves whose cell-bodies are in intimate connection centrally with the afferent visceral nerves and thus referred to areas on the body surface, the pain which accompanies visceral disease, has been characterized as

referred pain. Since it is referred to the zones of the body surface supplied by the connecting somatic sensory nerves, it is evident that it is not necessarily expressed over the diseased organ (Head (12, 13), Mackenzie (27)).

The sensory reflex from the lung rarely takes the form of a sharp pain, such as that caused by an acute inflammation in skeletal structures. Pain is, however, occasionally met in the skin-zones supplied by the midcervical nerves (Fig. 142); but a reflex change in sensation

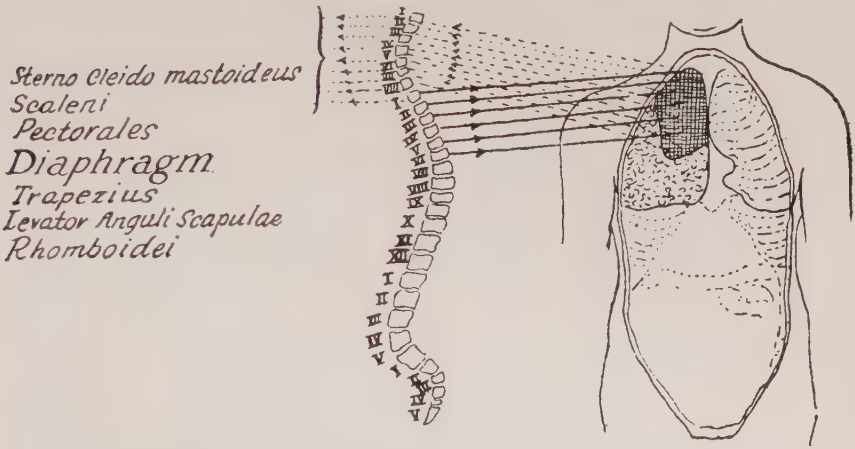

FIG. 141. Schematic illustration of pulmonary viscero-motor reflex. The lines running between the lung and the spinal cord represent sympathetic nerves. The solid lines carry innervation to the lung. The broken lines carry the impulses from the lung to the cord, where they are transmitted in the cervical portion to the spinal motor nerves, which complete the reflex. The muscles involved in this reflex are shown in the illustration. The path of the reflex is not, as shown in the illustration, directly from the lung to the cervical portion of the cord, but back to the upper six thoracic segments, thence upward to the cervical portion of the cord by intercalated neurones. ((58), p. 277.)

does not necessarily mean that an acute inflammation is present at the time. Lung pain is, rather, a change in sensation, resulting from injured sensory neurones with a lowered threshold of response, in which the inhibition of the higher centres has been lessened. Prolonged bombardment of the cord with harmful impulses from the lung renders the somatic sensory nerves so hyperirritable that they no longer have the power to withstand harmful impulses and to make a ready physiological adjustment to stimuli of a general nature. Since the inhibi-

tion of the higher levels is also broken down, the stimuli reach the sensorium over these injured neurones, which would, under ordinary circumstances, stop short of recognition. Under the same conditions uninjured neurones, associated with normal organs, react normally and maintain their physiological balance.

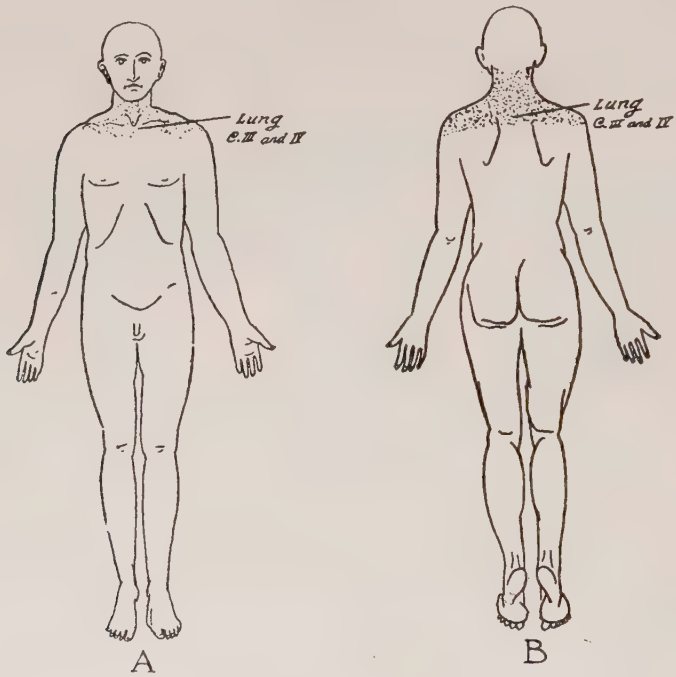

FIG. 142. Pulmonary viscero-sensory reflex. *A*, anterior view; *B*, posterior view. The third and fourth cervical sensory zones are involved, the same as those shown in the phrenic sensory reflex from the diaphragm; and on the right side the same as found in the hepatic viscero-sensory reflex. Cutaneous pain from the lungs is for the most part, if not wholly, expressed above the second rib (*A*), and the spine of the scapulae (*B*). ((58), p. 278.)

The sensory reflex from the lung is expressed as discomfort, soreness, or aching manifested under many conditions, such as fatigue, worry, discontent, fear, and other harmful emotions, due to changes in the weather, or to menstruation,—all of which call upon the patient for an extraordinary physiological adjustment. Except under unusual conditions, this reflex is restricted to those sensory somatic nerves

which arise from the midcervical segments of the cord. Since the reflex is expressed in the terminal endings of these nerves, it may affect the skin, the subcutaneous tissues in the areas shown in Figure 142, or the muscles, as shown in Figure 141. Thus, the deep pain of which the patient complains, may be accounted for,—such as the soreness and aching in the shoulders (in the trapezius and levator anguli scapulae); in the back (in the rhomboidei and trapezius); and in the front of the chest (in the pectorales),—soreness so common in tuberculosis. There seems to be no acute pain in pulmonary inflammations like that frequently found in the hollow organs, i.e., the stomach and intestines, biliary tract and ureter, or in the pleura and peritoneum.

Pulmonary Trophic Reflex of Sympathetic Origin in Somatic Structures

The pulmonary trophic reflex affects tissues co-extensive with those which show both the motor and sensory changes. It is present only after a disease process has existed for some time; and hence is an indication of chronicity. This reflex manifests itself as a lack of elasticity and a wasting of the affected tissues. The extent of the atrophy depends very largely upon the extent of the pulmonary disease, and is greatest in widespread lesions which have been active over long periods of time. It varies in different diseases, being found most commonly and quite regularly in chronic pulmonary tuberculosis. It is scarcely recognizable in chronic bronchitis, whether or not accompanied by bronchiectasis; in fact, these affections may usually be differentiated from chronic tuberculosis by the slightness, or the apparent absence, of the trophic reflex.

The trophic reflex in the skin and subcutaneous tissues is apparently confined to the skin-zones innervated by the third, fourth and fifth cervical nerves (40; 41; 47; 54; and 58, p. 280). This is the area extending from the second rib anteriorly and the spine of the scapula posteriorly to the chin and base of the skull (Fig. 143, *A* and *B*).

In the muscles, the trophic reflex follows the same segmental distribution, but covers a wider area; for the muscles innervated by the third, fourth and fifth cervical nerves comprise the important muscles of the shoulder girdle, the broad muscles covering the anterior and posterior portion of the thoracic cage and the crus and central tendon of the diaphragm.

The skin where the trophic reflex is shown, is thinner than normal

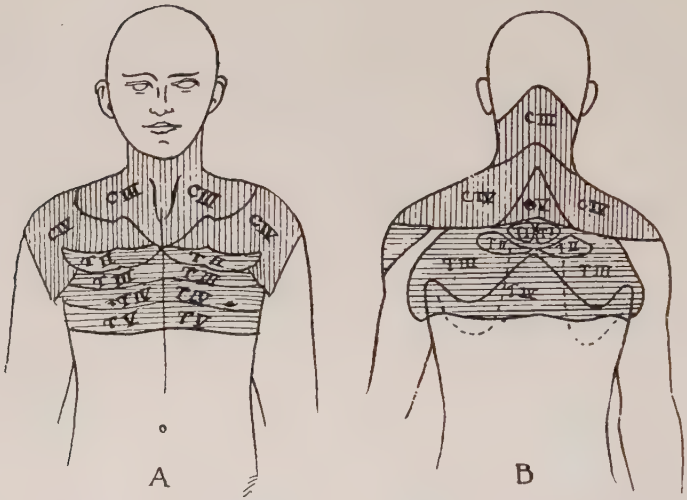

FIG. 143. Photograph showing by vertical lines the cutaneous and subcutaneous areas which are affected by the pulmonary viscero-sensory and viscero-trophic reflexes.

A. Anterior view. This viscero-trophic reflex is shown particularly as a degeneration of the skin and subcutaneous tissues supplied by the third and fourth, and slightly by the fifth cervical sensory roots. It will be seen that anteriorly this includes the tissues of the neck, shoulders, and chest down as far as the second rib.

B. Posterior view. This includes the neck, shoulders, and that portion of the chest above the spine of the scapulae. The interscapular tissues involving TI, TII, TIII, and TIV show the hilus saucer of degeneration. Degeneration in areas is marked by horizontal lines caused by old pleural involvement. ((58), p. 283.)

FIG. 144. Photograph showing the pulmonary and pleural trophic reflexes. This patient had a very extensive right-sided pulmonary tuberculosis of a chronic nature. He also had a less extensive, though chronic, lesion on the left side. He had a very marked pleuritis on the right side anteriorly, and at the left base posteriorly.

A. Anterior view. This shows the degeneration of the muscles, skin and subcutaneous tissue over the entire right side, most marked from the angle of the jaw to the nipple. The fact that atrophy extends below the second rib as well as above it indicates that both the lung and parietal pleura have been involved in chronic inflammation. On the left side the degeneration is less marked in the muscles, skin and subcutaneous tissue and extends very little below the second rib. This is predominantly a pulmonary reflex, with little involvement of the parietal pleura.

B. Posterior view. It will be noted that the degeneration of the muscles, skin, and subcutaneous tissue above the spine of the scapula is present on both sides, though more marked on the right. The parietal pleura is involved at both apices, and at the left base.

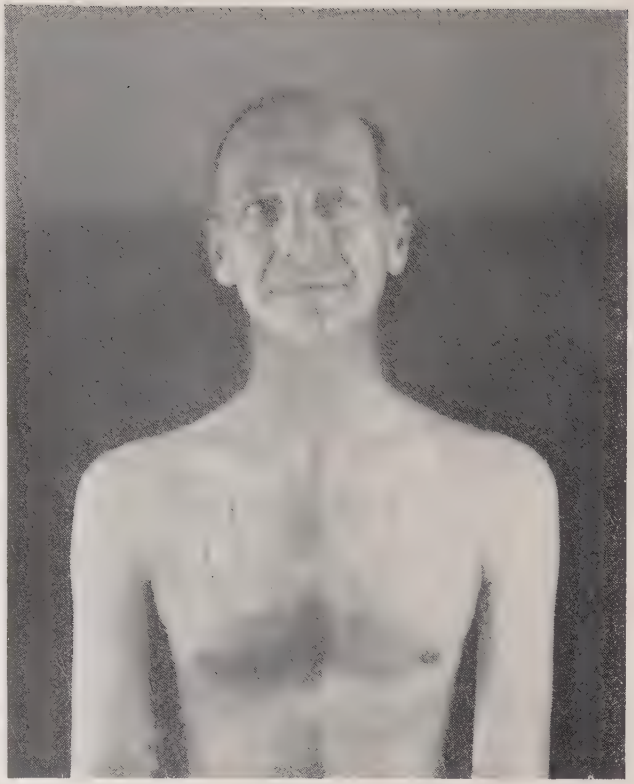

Fig. 144A

Fig. 144B

and less elastic. The subcutaneous tissues actually disappear, as is shown in Figure 144, *A* and *B*. The space between the skin and the underlying muscles or bones is less than normal, as may be determined by a comparison with the subcutaneous tissues in zones not affected by the reflex. The skin accordingly is not bound down so closely and consequently it can easily be picked up between the thumb and fingers and lifted away from the underlying tissues.

The muscles become smaller, as shown in Figure 144, often losing quite a percentage of the substance between their bundles and becoming more stringy than normal. A characteristic of all the tissues involved in the trophic reflex is that they become less elastic and present an edematous or doughy surface to the palpating fingers.

DISTRIBUTION OF PULMONARY PARASYMPATHETIC REFLEXES IN SOMATIC STRUCTURES

Clinical evidence seems strongest in favor of the theory that pulmonary reflexes in the somatic structures, innervated by the midcervical segments of the cord, are probably produced by stimuli carried centralwards over sympathetic nerves, although there are still other reflexes in somatic structures for which the stimuli pass centralwards over the vagus.

The relationship between the vagus and the other cranial nerves is similar to that which exists in the cord between the sympathetic and the spinal nerves. In fact, the bulb must be looked upon as an expanded, or even distorted, portion of the cord. Here the same mediation of reflexes takes place from viscera to somatic structures, from somatic structures to viscera, and from viscera to viscera, as has been observed at other levels in the cord.

When the pulmonary tissue is inflamed, the phenomena expressed reflexly in the cranial region of the body through the parasympathetic nerves, are of the same nature as those expressed in the neck and trunk regions through the sympathetic nerves, namely: (*a*) motor, (*b*) sensory, and (*c*) trophic changes. In the case of the vagus nerve, however, somatic effects seem to be produced largely, if not wholly, through efferent cranial nerves; and, with the exception of the sternocleidomastoideus and trapezius muscles, they appear to be confined to the cranial structures.

Pulmonary Motor Reflexes of Parasympathetic Origin in Somatic Structures

Through stimuli which pass from the lung over the vagus and are transferred to the spinal accessory nerve, the sternocleidomastoideus and trapezius muscles are thrown into spasm when the lung is inflamed. These two muscles are also influenced by stimuli carried by the sympathetic nerves. The spinal accessory nerve appears to be more important than the spinal nerves in affecting the sternocleidomastoideus; while the spinal nerves are chiefly responsible for reflex action in the trapezius (Rasmussen (59)). In addition to the motor reflex from the lung so readily detected in the two important muscles of the shoulder girdle (the sternocleidomastoideus and the trapezius) there are also to be noted the vasomotor effects, such as the flushing of the face, produced through the sensory fibers of the trigeminus. It is also safe to assume that the trigeminus and facialis nerves carry somatic motor reflexes of vagus origin to the facial muscles ((58), p. 295), since these muscles atrophy as a result of long-continued inflammation in the lung. This is very evident in a small percentage of chronic lesions in which the inflammation is largely confined to one lung.

Pulmonary Sensory Reflex of Parasympathetic Origin in Somatic Structures

Certain sensory changes are produced when the lung is inflamed. These changes occur in the tissues innervated by the sensory portions of the trigeminus, whose cell-bodies are intimately connected with the afferent pulmonary fibers of the vagus. Sometimes these are manifested as headache, sometimes as face-ache, occasionally as soreness, or simply as discomfort. At times these sensory changes are confined to the brow of the vertical and temporal areas; at other times they extend downwards over the cheek.

Pulmonary Trophic Reflexes of Parasympathetic Origin in Somatic Structures

The trophic changes in somatic structures, which are expressed reflexly through afferent parasympathetic neurones, are not detected so constantly, neither are they so easily determined as those expressed over the sympathetic nerves. In certain patients in whom the pulmonary involvement is extensive, of long duration, and largely limited

to one lung, *the atrophy of the facial muscles* through the trigeminus and facialis is readily seen. It is often noted on simple inspection and is distinctly visible when the patient is required to show the teeth or smile. Usually the phenomenon is very slight; although it may be so marked as to suggest a central nerve lesion. This atrophy is not recognized more generally because it is not expected; and the idea of a reflex cause would not be the obvious explanation. For patients with advanced tuberculosis often show a wasting of the body; and the thin face is supposed to be a part of the picture. Furthermore, pulmonary tuberculosis usually involves both lungs, producing effects in the muscles of both sides of the face and thus leaving no norm for comparison.

REFLEXES OF PULMONARY ORIGIN EXPRESSED IN OTHER VISCERA

In considering the lung as an organ causing reflex activity in other viscera, it is important to remember its embryological origin from the enteral system. The very close reflex connection between the different parts of the gastro-intestinal tract has been shown by Pearcy and his co-workers (36). This connection apparently includes the lung,—to judge from the many reflex disturbances in the gastro-intestinal canal resulting from an inflamed lung. Hence the segmental relationship noted between the lung and the somatic structures also exists between the lung and other viscera.

Viscero-Visceral Sympathetic Reflexes of Pulmonary Origin

The gray matter of the midcervical segments of the cord contains the principal centres for pulmonary somatic reflexes; but inasmuch as there are no lateral horn cells in the cervical portion of the cord, the mediation of afferent sympathetic stimuli for the production of sympathetic reflexes in other viscera, must take place elsewhere.

The paths by which the lungs influence other viscera, when both afferent and efferent impulses are carried over sympathetic neurones, are probably determined in the same manner as in the case of the viscero-somatic reflexes,—by Sherrington's segmental law and the law governing the spread of reflexes. In this connection the fact must be considered that since there are no sympathetic fibers arising in the midcervical segments of the cord, the lung must bear a different segmental embryological relationship to the viscera from that which it bears to the somatic structures. Thus the closest reflex relationship

between the lung and the other viscera, over the sympathetic nerves, is through intrasegmental neurones whose cell-bodies lie in the upper five or six thoracic segments; while the somatic relationship is furnished through intersegmental paths between the upper dorsal and the midcervical segments.

One of the most evident pulmonary sympathetic reflexes is *the dilatation of the pupil*, as found in pulmonary tuberculosis. Here the afferent impulse is carried centralwards over the pulmonary sympathetic fibers to the upper thoracic segments of the cord, where it enters Budge's centre for papillary control. This centre lies in the upper thoracic and lower cervical segments. The efferent component of the reflex, which is also a sympathetic neurone, carries the impulse to the superior cervical ganglion where non-medullated fibers arise which pass on to the Gasserian ganglion. Here it joins fibers of the ophthalmic branch of the fifth nerve and courses with it to supply the vessels of the eye, the dilator muscle of the pupil, and the Müllerian muscle.

The author has also seen, as symptoms in pulmonary tuberculosis, instances of *oversympathetic activity which caused lessened motility and secretion in the gastro-intestinal tract*; *increased sphincter activity*; and disturbances in cardiac activity (tachycardia, Fig. 145),—all of which seemed beyond question to be of a reflex nature from the inflamed lung. This reflex action is not taken into sufficient consideration in the explanation of clinical phenomena. Examples of this character are seen in the relaxed gastric musculature, with the open cardia permitting the eructation of gas and the regurgitation of food in patients with advanced tuberculosis, and especially during periods of prolonged toxemia. The possibility of reflex inhibition in the liver and pancreas must also be kept in mind.

Viscero-Visceral Parasympathetic Reflexes of Pulmonary Origin

Visceral reflexes caused by stimuli coursing both centralwards and peripheralwards over parasympathetic neurones, are fairly well recognized. In this group are spasms of the gastric and intestinal musculature due to irritation from an inflamed appendix or gall-bladder; reflex disturbance of heart-action (bradycardia); and asthma arising reflexly from stimuli in many organs.

Many reflexes from different viscera in which the impulses are carried centralwards over the vagus and then transmitted to other

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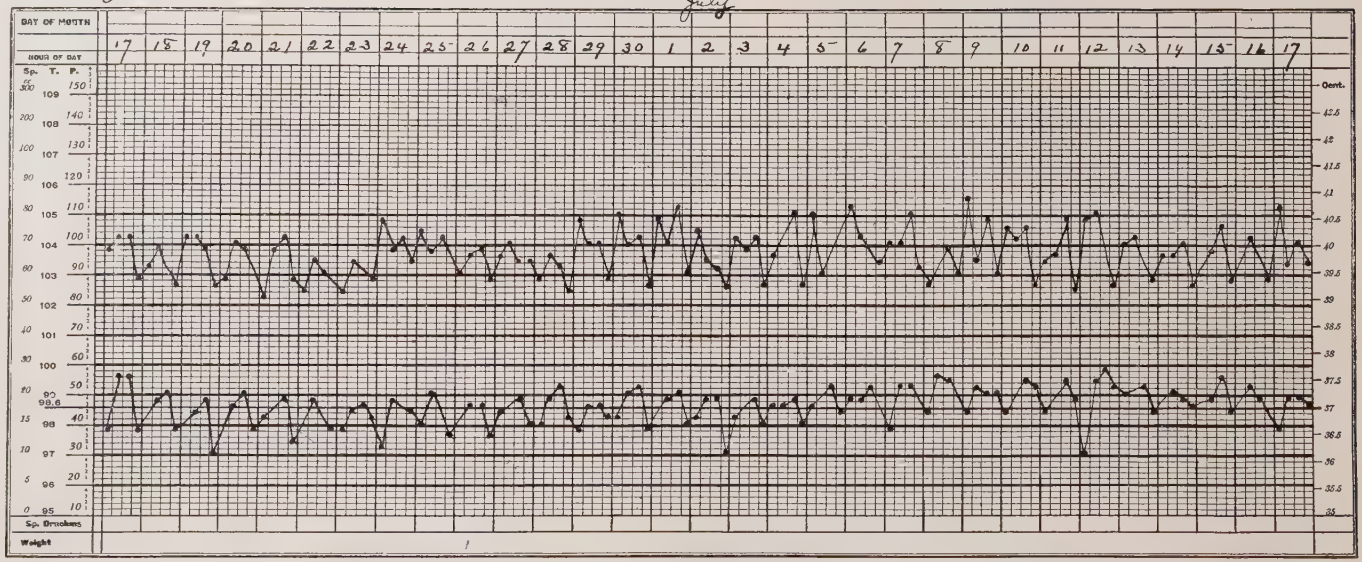

FIG. 145. Chart illustrating tachycardia in a case of quiescent tuberculosis. Lower curve, temperature; upper curve, pulse.

It will be noted that the rate of heart-beat is entirely out of harmony with the height of the temperature-curve. It will also be noted that the pulse-rate is very unstable. This was due to the fact that the patient had a poor nerve-balance, and also that she was on exercise. The increase in temperature shown in the last third of the chart is the premenstrual curve.

visceral fibers of the same nerve, have long been recognized under the name of functional symptoms. Afferent vagal fibers carry from the lung impulses which affect disturbances in the normal activity of many other viscera.

The larynx shows three distinct phenomena which are produced reflexly by impulses transferred centralwards over the pulmonary branches of the vagus and then peripheralwards over the superior and inferior laryngeal branches of the vagus. The first is the sensory impression which is recognized as *a laryngeal irritation* and causes the patient to clear the throat and cough. This reflex is transferred to the larynx over the superior laryngeal nerve. It is a very common phenomenon in all diseases of the lung and bronchi.

Motor reflexes are mediated with both the superior laryngeal and inferior laryngeal nerves. They result in *hoarseness* and at times, *aphonia*. The reflex produced by the superior laryngeal nerve is occasioned by a failure of the cords to become approximated, on account of an unequal stretching of the two vocal bands. The reflex caused by the impulse coursing over the inferior laryngeal nerve, leads to a disturbance of the abductor muscles, which in turn produces a faulty approximation of the cords.

The cough is a very complex reflex in which the impulse is carried centralwards over the vagus and transferred peripheralwards to all the expiratory muscles, with a simultaneous inhibition over all the nerves supplying the inspiratory muscles.

The rhinopharyngeal secretion is often increased, as a result of pulmonary tuberculosis, in such a manner as to make the reflex relationship extremely suggestive.

The flushing of the face is due to a transference of impulses from the vagus to the sensory fibers of the trigeminus nerve, and is thus produced by the same sort of vasodilatation that occurs with the central stimulation of other sensory nerves, such as the sciatic.

A bradycardia is often found in patients suffering from tuberculosis, particularly in those of the vagotonic group (Figs. 146 and 147). But even in those who have no particular vagotonic tendencies, a reflex slowing of the pulse is occasionally caused by the inflamed pulmonary tissue. The author has noted this symptom at times when the lung was the seat of a marked allergic reaction. Brodie and Russell (4) have even found that the central stimulation of the pulmonary branches of the vagus slows the heart more than does the direct stimulation of the cardiac fibers.

TEMPERATURE CHART

DATE July NAME August NO.

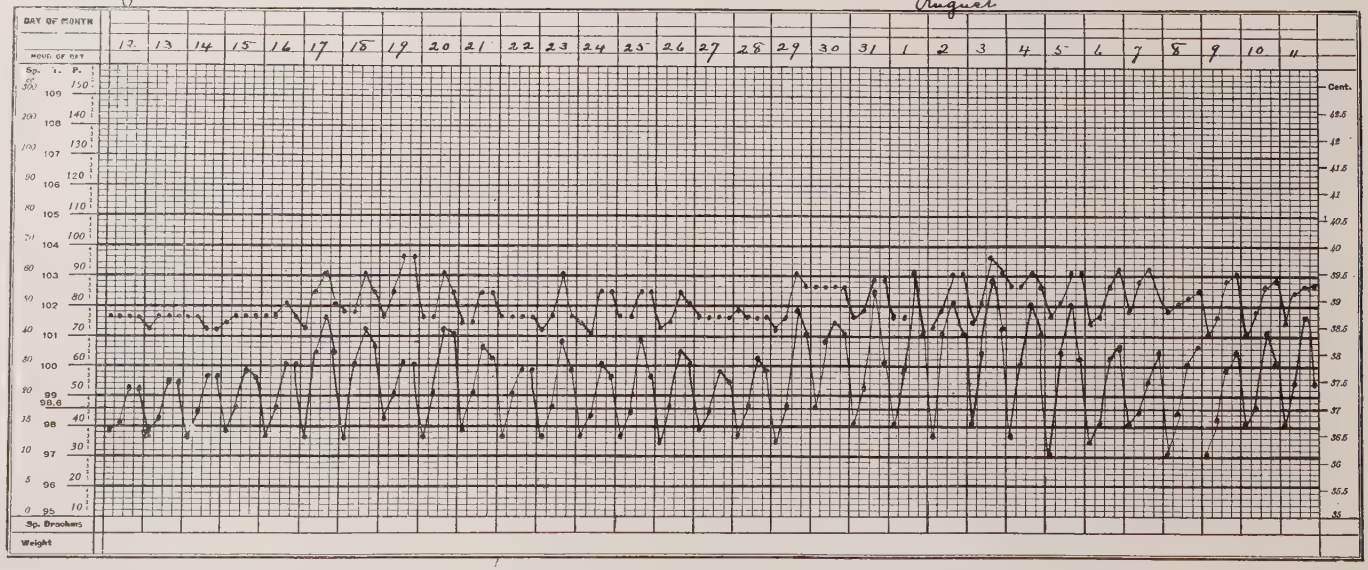

FIG. 146. Chart illustrating reflex bradycardia in the presence of severe inflammatory reaction in the lung with cavity formation. Lower curve, temperature; upper curve, pulse.

It will be noted that the pulse is much lower than would be expected under the circumstances; also, that it did not respond at the times when the temperature went the highest. In order to maintain the low level the reflex effects coming over the vagus nerve were obliged to counteract the sympathetic effects due to the toxins, and those due to reflex impulses, together with the effects of any of the harmful emotions that accompanied the severe reaction. ((58), p. 290.)

TEMPERATURE CHART

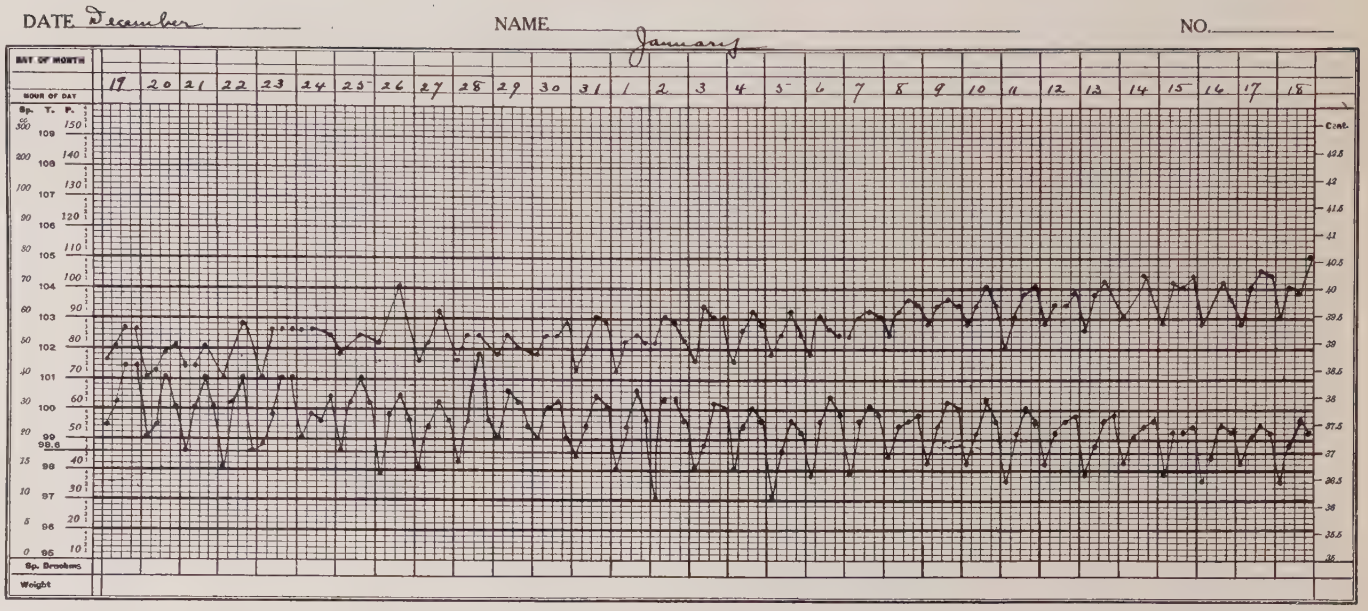

FIG. 147. Chart illustrating bradycardia in a patient suffering from active tuberculosis. Lower curve, temperature; upper curve, pulse. The chart shows how inflammation in the lung reflexly slows the heart. The afferent impulses course through the pulmonary, and the efferent through the cardiac branches of the vagus nerve.

At the beginning of the month, with a temperature of 101°, the maximum pulse for the day was between 80 and 90. The inflammation gradually subsided and at the end of the month the temperature was between 90° and 100°, but the pulse had increased, the maximum for the day being between 100 and 110. This chart shows the pulse becoming progressively more rapid as the inflammation in the lung progressively decreased and the reflex stimulation of the vagus lessened. ((58), p. 291.)

The spastic colon and increased motility are frequent accompaniments of pulmonary tuberculosis. The impulses responsible for the phenomena are transferred from the pulmonary to the intestinal branches of the vagus.

Numerous reflex effects produced in the gastro-intestinal canal may be observed during a course of chronic inflammation such as tuberculosis. They vary from time to time, with the many changes in pathology and their different degrees of inflammatory reaction. Among the most noticeable of these effects are cardiospasm, open cardia, pylorospasm, increased motility, lessened motility, reversed peristalsis, changes in secretory activity. It may also be assumed that some of the changes wrought in the pancreas and liver are of a reflex nature; although alterations may also be caused by such constitutional factors as toxemia, and variations in the acid- and salt-balance.

Viscero-Trophic Reflexes

No doubt many of the disturbances encountered in other organs when the lung is inflamed, are due to the fact that the central cells of the neurones supplying these organs have been injured by the long bombardment with excessive stimuli, occasioned by the chronic inflammation in the lung. While these suppositions cannot be accepted as proven facts, yet they must be given some support. Such disturbances include the motor and trophic effects in the somatic structures, produced through the spinal and cranial neurones which mediate pulmonary reflexes. *The atrophy of the tongue*, which is seen at times (Fig. 148), is due to a reflex mediated through the hypoglossus. This symptom has been noted in several instances to so marked a degree that when the organ was protruded it would push over toward the degenerated side. In these cases inspection has shown the atrophied half to be not so large or so well rounded as the normal side.

Three other such trophic reflexes have been suggested as physiological possibilities and as clinical probabilities. Such a reflex may occur (*a*) in the larynx, (*b*) in the intestine, or (*c*) in the rhinopharyngeal structures.

Tuberculosis of the larynx is usually secondary to that of the lung. In patients suffering from a pulmonary tuberculosis where the lesion is predominantly confined to one lung, or where one lung has been the seat of the disease for a much longer time than the other, the laryn-

geal lesion, if one-sided (as is often the case), is usually found on the side corresponding with the more extensive or older pulmonary lesion. Realizing the trophic disturbances caused in other tissues, the author

FIG. 148. Trophic reflex shown in the tongue. This patient suffered from a chronic pulmonary tuberculosis, largely confined to the left lung. The disease was of several years' duration. It will be noted that on protruding the tongue, not only is the left side smaller than the right, but the tongue pushes over toward the left side. Atrophy of the facial muscle, also, shows to a slight extent on the left side.

suggested that a contributary cause of laryngeal tuberculosis was in all probability a lowering of the resistance in the tissue, caused by the long-continued assaults upon the larynx with reflex stimuli from the lung ((56, p. 22).

The intestinal tract bears a similar relationship, except that the analogy cannot be so strong because it lacks the two-sidedness of the larynx. In all probability, the same line of reasoning holds. The long-continued invasion of the gastro-intestinal tract with reflex impulses probably lowers its vitality and favors the implantation of bacilli in those areas, the lower ileum and ascending colon, where the bacillus-containing intestinal contents are retarded and the bacilli are consequently brought into more intimate and more prolonged contact ((56), p. 37). Here again analogy with the somatic structures supports the suggestion; for while all the tissues of the body waste as a result of chronic tuberculosis, there is an exaggerated wasting in all the visible areas that are influenced reflexly by impulses coming from the lungs ((58), p. 280).

The same explanation may doubtless be applied in the case of the trophic reflexes occurring in the rhinopharyngeal structures.

Sensory Reflexes

Laryngeal irritation through the superior laryngeal nerve is one of the most common reflexes from the lung. It begins with the early inflammatory reaction in the pulmonary tissue, and is further augmented by secretions in the air passages as well as by the adhesions and contractions resulting from the disease.

RELATION OF TOXIC SYMPTOMS TO THE VEGETATIVE NERVES

Early in the author's study of the vegetative nervous system he saw that all the symptoms of tuberculosis could be grouped into three classes, according to the etiological factors responsible for them (42, 43, 46): (*a*) those due to toxemia, or general symptoms; (*b*) those of reflex origin; and (*c*) those due to the tuberculous process *per se*, as shown in Table X.

Analysis shows that the vegetative nerves are implicated in the production of every symptom in the toxic or general group, in all of those of the reflex group, and in a part of those caused by the tuberculous process *per se*. Further consideration demonstrates that this grouping of symptoms is applicable to all the infections involving important organs.

The effect of toxins is not confined to the vegetative nerves, but is expressed elsewhere in the nerves, in the glands of internal secretion, and in the cells of the body. Increased sympathetic activity is,

however, pronounced in the particular syndrome of increased temperature, rapid heart-beat, decreased motility and secretory activity in the gastro-intestinal tract, vasoconstriction in the skin-capillaries, pilomotor effects, sweating, and leucocytosis (43; and 58, pp. 126–128). The following symptoms may also be included in this category: the dry burning eyes, the dryness of the throat, the decrease in watery

TABLE X

ETIOLOGICAL CLASSIFICATION OF SYMPTOMS OF PULMONARY TUBERCULOSIS

GROUP I	GROUP II	GROUP III
Symptoms Due to Toxemia and Other Causes Acting Generally	Symptoms Due to a Reflex Cause	Symptoms Due to the Tuberculous Process *Per Se*
Malaise	Hoarseness	Frequent and protracted colds (tuberculous bronchitis)
Lack of endurance	Tickling in larynx	Spitting of blood
Loss of strength	Cough	Pleurisy (tuberculosis of pleura)
Nerve instability	Digestive disturbances (hypermotility and hypersecretion through vagus, or hypomotility and hyposecretion through sympathetic nerves, also disturbance in the cardiac and pyloric sphincters) which may result in loss of weight	Sputum
Digestive disturbances (hypomotility and hyposecretion)	Circulatory disturbances	
Metabolic disturbances resulting in loss of weight	Chest and shoulder pains	
Increased pulse-rate	Flushing of face	
Night sweats	Spasm of muscles of shoulder girdle	
Temperature	Diminished motion of affected side	
Blood changes		

elements of the saliva, and the inhibiting effect upon the muscular activity in the bronchi. The last-mentioned phenomenon is frequently very pronounced. It is consequently of interest to note several occasions where relief from asthmatic paroxysms has been caused by acute infections such as tonsillitis, pneumonia, influenza, and typhoid fever (48).

PARASYMPATHETIC REFLEXES EXPRESSED IN THE LUNG WHERE THE STIMULUS ARISES IN OTHER ORGANS AND IS CARRIED CENTRALWARDS OVER THE PARASYMPATHETIC NERVES

The lung may show two reflexes, *asthma* and *bronchitis*, which are produced by stimuli arising in other organs. Asthma is a condition of increased parasympathetic action involving the bronchial musculature, and bronchial secretory glands. It is characterized by vasodilatation and edema of the tissues (44). Bronchitis is usually associated with it.

Bronchitis, on the other hand, is an increased parasympathetic activity, affecting particularly the secretory glands of the bronchi. In the latter affection, however, increased muscular action is not a prominent part of the picture.

Both of these conditions may result reflexly from impulses arising in other viscera. In an individual predisposed to asthma, the affection may result from nasal irritation, and the paroxysm may be relieved by the cocainization of the nose. Or the attack may be precipitated by reflexes arising in other organs, such as the heart, liver, gall-bladder, the gastro-intestinal canal, the kidney; by an impulse arising, in fact, in any organ or tissue which may mediate with the pulmonary branches of the vagus (48, 52).

Reflex bronchial secretion is not so easily stimulated alone, but usually in conjunction with the bronchial musculature. It is, however, important to remember the existence of pathways for the reflex production of bronchitis as a result of stimuli arising in other organs, such as the heart, stomach, intestine and liver.

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CHAPTER XXVIII

THE RELATION OF THE VEGETATIVE NERVOUS SYSTEM TO HYPERTHYROIDISM[1]

GEORGE W. CRILE, M.D.

INTRODUCTION

THE nervous system may properly be considered as comprising not only those organisms and structures generally included in the central and vegetative nervous systems but also the adrenal and the thyroid glands since the latter together with the former control the adaptive energy transformation of animals. Adaptive energy transformation is the one outstanding factor that distinguishes the plant from the animal. An animal may be regarded, therefore, as a higher plant, to the equipment of which has been added a mechanism for adaptive energy transformation; that is, the transformation of potential into kinetic energy. This system may not illogically be designated as a "kinetic system."

The most outstanding and unique example of a continued activation of this group of organs, which results in continued increase in energy transformation, is a state of hyperthyroidism,—more appropriately designated "hyperkineticism."

In hyperthyroidism not only is there a continued increase of energy transformation but from time to time there appear crises during which the transformation of energy is temporarily augmented still further. It is proposed to discuss the nature of these thyroid crises and their exciting causes, the mechanism that produces them, their peculiar setting, and the factors that govern them, and to offer evidence in support of the conception that hyperthyroidism is not primarily a disease of the thyroid gland but is rather a disorder of the entire kinetic system as defined above. In a thyroid crisis the organism is driven so intensively and its functions are so magnified that the crisis serves as a physiologic microscope through which are revealed more clearly certain functions of certain organs.

[1] From the Cleveland Clinic, Cleveland.

THYROID CRISES

The clinical analysis of a thyroid crisis shows that it can be precipitated by any one of only eight factors, six of which are intra-organic, that is, originate within the organism itself; while two may be applied artificially. The six inherent factors are: (*a*) emotional excitation, such as fear, anger, worry; (*b*) foreign and split proteins, such as infection, wound secretion; (*c*) asphyxia; (*d*) hemorrhage; (*e*) pain; (*f*) physical exertion. The two artificially produced factors are: (*a*) the induction of inhalation anesthesia; and (*b*) the injection of adrenalin.

Whether the crisis is precipitated by a single one or by several of these factors, or whether it occurs merely in the natural course of the disease, the symptoms, and in fatal cases the mode of death, are identical. There must be, therefore, some common cause which is activated by these divergent exciting conditions. What common factor in asphyxia, hemorrhage, physical injury, physical exertion, emotional strain, or infection, is responsible for the thyroid crisis? Exclusive of the injection of adrenalin, each of the factors enumerated above produces an increased output of the specific hormone of the adrenal glands, as has been proven by the researches of Cannon and others (1, 2), as well as by the author (3, 4), whose experiments have shown that the adrenal glands are influenced by every activation of the central nervous system.

Moreover it is significant that no other natural factor such as rest, sleep, food and water, heat or cold, and no drugs such as sedatives, narcotics, digitalis, strophanthin, atropine, sodium bicarbonate, glucose, cathartics, calcium or magnesium, can produce a thyroid crisis. Even the injection of iodine or of thyroid extract cannot produce a thyroid crisis. Moreover in the absence of the thyroid gland or when, after thyroidectomy, hyperthyroidism has been replaced by myxedema, each of these specific excitants loses its effect. In the absence of the thyroid gland or in myxedema the injection of adrenalin loses its specific effect. A thyroid crisis under such conditions cannot be produced even though any of these factors may destroy the organism and produce death.

SYMPTOMS OF HYPERTHYROIDISM

The symptoms of hyperthyroidism and of the crises of hyperthyroidism are identical with those of hyperadrenalism,—dilated

pupils, flushed skin, sweating, increased metabolism, increased action of the heart. The injection of adrenalin in itself alone produces these symptoms, each of which is present in hyperthyroidism; and the injection of adrenalin in the presence of hyperthyroidism causes an increase in every one of them. These symptoms in themselves betray the intermediary between the adrenal glands and the thyroid gland. The adrenal glands act through the nervous system upon the thyroid gland; the thyroid gland acts through the nervous system upon the adrenal glands—each of these three organisms depends upon the other two. It is for this reason that the ductless glands are regarded as being inherent parts of the nervous system itself.

Further evidence that the nervous system, the adrenal glands, and the thyroid gland cannot be considered alone, is found in the following facts: (*a*) hyperthyroidism has never been seen in a case of Addison's disease; (*b*) the excision of one adrenal gland temporarily lessens the symptoms of hyperthyroidism to a degree comparable to the removal of one lobe of the thyroid gland; (*c*) in myxedema, adrenalin loses most of its physiologic effect; (*d*) deep narcotization with morphine nullifies the effect of adrenalin; (*e*) no case of hyperthyroidism has been observed in a cretin or in the presence of a normal thyroid gland; (*f*) the division of the nerves supplying the thyroid gland considerably controls the disease; (*g*) physiologic rest is of profound benefit; (*h*) excitation of the nervous system is the most potent cause of the disease and of its crises. Finally, of the eight factors enumerated above six are specific and may cause a crisis of hyperthyroidism. They are also the common exciting causes of the disease. These six factors produce their protean effects primarily by activating the nervous system which in turn activates the thyroid gland and the adrenal glands. One might as well try to separate the nucleus and the cytoplasm of a cell, or the negative and positive plates of a battery and expect either to operate, as to expect the adaptive transformation of energy to continue in the absence of the nervous system, of the adrenal glands, or of the thyroid gland; for each one of these is an essential part of the organic machine.

It would seem more profitable to identify and study the energy-transforming system as a whole, and to find some new designation for the disease, rather than to relate it to a single organ which does not originate it, but merely collaborates in its origin and in its continuation.

The outstanding characteristic of hyperthyroidism is the facilitation and acceleration of the production and discharge of potential energy by means of the collaboration of a definite group of organs. As a result of this acceleration the energy-transforming system is speeded up, and for this reason it would appear that a better term than hyperthyroidism to apply to the disease, would be "hyperkineticism." This name does not assume that all the factors involved in this protean disease are understood but that it would seem more descriptive than the present term.

Certain experimental evidence as to the interrelation of the nervous system, the adrenal glands, and the thyroid gland may now be considered.

EXPERIMENTAL WORK

Years ago it was found by the author that the administration of iodine or of thyroid extract, produced an early hyperchromatism of the brain-cells followed by progressive chromatolysis. A single dose of adrenalin produced hyperchromatism of the brain-cells; the repeated administration of adrenalin was followed by their chromatolysis. The remarkable significance of these findings has been greatly enhanced as a result of the experiments now being conducted in the laboratories of the Cleveland Clinic by Dr. Beutner, who has found that the stainability of cells is apparently a direct indication of their electromotive force or potential. Dr. Beutner is investigating this point by the construction of certain artificial systems or organic substances, which react to different stains as do the hyperchromatic and hypochromatic brain-cells and which also produce an electromotive force varying with their stainability just as the electromotive force of a tissue varies with its stainability.

Since iodine is the essential content of the product of the thyroid gland, and in view of its specific effect on metabolism, it might be suspected of governing the electric permeability of the cells of the body. In the author's own researches (4) it was discovered that after a latent period of twelve or more hours, iodine and thyroid extract each increases the electric conductivity and capacity of the organs and tissues of the body, of the brain in particular. In physical terms the change in the conductivity and capacity of a tissue signifies a change in its activity. These physical changes, like the clinical changes due to thyroid activity, are lasting and not fleeting. Increased con-

ductivity and capacity are associated with increased functional activity. These changes alone would augment oxidation, and hence, basal metabolism.

These findings are comparable to those in similar physical measurements of plants, of growing tumors, of fertilized ova, and of the ameba. It may be urged that what have been measured, are changes in the concentration of the electrolytes in the tissues or in the blood-supply. It is true that these variations in conductivity and capacity, are in part due to changes in electrolytic concentration. Such changes in electrolytic concentration, however, constitute an essential part of the mechanism of stimulation and appear coincidentally with those in the permeability of the cell-membranes. Moreover, in these experiments, changes in conductivity and capacity have been found in tissues after death, when they must be independent of the circulation. These electrical changes run parallel with the clinical phenomena.

The experiments have shown that the effect of adrenalin on the capacity and conductivity of tissues and organs is wholly different from that of thyroid extract and of iodine; that is, while the effects of thyroid extract and of iodine are not manifested until after a considerable latent period, the administration of adrenalin causes an immediate and striking change in capacity, temperature, and conductivity. Moreover, the effects of adrenalin last for only a few minutes while those of thyroid extract and of iodine last for hours and days.

The most striking characteristic of the adrenalin effect, however, is its unexpected selective action on the organs and tissues of the body; that is, adrenalin produces a sharp rise in the conductivity, temperature and capacity of the nerve-tissue, but shows the opposite effect on the conductivity, temperature and capacity of all other tissues, with one notable exception,—namely, the medulla of the adrenal gland itself. At first this highly selective action of adrenalin on the tissues and organs seemed incomprehensible until it occurred to the writer that differences in the potential of the organs of the body might well depend upon this very effect.

It might be expected that iodine and thyroid extract would raise the potential of the cells, and experiments performed in the laboratory have proven such to be the case. If iodine or thyroid extract increases the capacity of the cells and also their electric load then it would be expected that the adrenal and the nervous system would discharge the cells; and the experiments have shown this to be the case.

RESULTS OF EXPERIMENTS

As a result of these experiments it would appear that the organism has been evolved on the principle of electric control, and that it is the function of the adrenal glands and of the vegetative nervous system to establish and to maintain and adaptively to change the differences in potential between the different organs and tissues, in order to meet the conditions of struggle and survival, such as fighting or escaping, mating and procreating, combating infection. If this conception be true, then not only is there a collaboration between the adrenal glands and the thyroid gland, but also among all of the organs and tissues concerned with the struggle of life as well as with the maintenance of life itself. In accordance with this conception, if the difference in potential between various organs and a neutral tissue such as fascia, were to be measured, it would be expected that during life and consciousness a certain difference would be found to exist and that at death this difference would be cancelled. It would be expected that adrenalin would specifically alter differences in potential in the normal animal and that in myxedema it would exert little effect on the difference in potential. It would be expected that alterations in potential would be related to the physiologic activity of the various organs; and that the activity of the organs would be related to the thyroid hormone, which controls the conductivity for longer periods, and to adrenalin, which controls the conductivity for shorter periods. These theoretical assumptions have been proven to be facts by the laboratory experiments of Dr. Telkes and Miss Rowland.

It may be assumed that the thyroid hormone, by increasing the permeability, increases the activity of the cells and organs,—of the brain, in particular. Increased permeability would make more effective every kind of stimulation. This would be one of the essential factors in nervousness,—perhaps the mechanism by which it is produced.

In myxedema, on the other hand, the conductivity, capacity and potential are decreased far below the normal level; and as a consequence, the permeability, hence the facility of stimulation, is decreased proportionately. This would explain the decreased metabolism, the depressed facility for stimulation and the decreased bodily activities—dullness and lethargy—in clinical cases of myxedema. As a climax to these observations it has been noted by the author that when an animal is in myxedema, adrenalin has lost

its striking control over the conductivity, capacity and potential,—a finding which parallels clinical observations as to the lack of effect when adrenalin is injected into myxedematous patients.

Moreover, and of peculiar significance, has been the discovery of a specific reaction of the medulla of the adrenal gland itself to the injection of adrenalin. It has been found that the injection of adrenalin into the vein of the ear of a rabbit causes a sharp rise in the conductivity and the capacity of the medulla of the adrenal gland—this effect being as striking as that of adrenalin on the brain, and in the same direction. It would appear from this finding that the medulla of the adrenal gland functions as nerve-tissue; perhaps it is the brain of the vegetative system, its probable action being to charge, to energize, the vegetative system. The embryologic origin of the medulla, the type of its cells and the kind of tumors that arise in it, all point to the same inference.

In his illuminating work on the adrenal gland and in his interpretation of its function along the lines of evolution, Cannon (1, 2) surely took an important step in the direction of this conception. If the belief, based upon clinical and experimental investigations, is correct that the single agent causing the acute exacerbations of hyperthyroidism, is the adrenal gland, then it would follow that by the removal of one adrenal gland in cases of hyperthyroidism, the factor of safety of the patient should be increased; that is, the removal of one adrenal gland, like the removal of one-half of the thyroid gland, should reduce the phenomena of hyperthyroidism. It may at once be objected that the factor of safety of the adrenal tissue is so great that the removal of one adrenal gland would show no effect. In normal cases this would be true, but in hyperthyroidism, the adrenal glands, like the thyroid, have had the factor of safety fully taken up by excessive action. One would therefore expect, in accordance with the writer's conception at least, that by the removal of one adrenal gland, as by the removal of one-half of the thyroid gland, the hyperthyroid phenomena would be correspondingly reduced.

The author has removed one adrenal gland in each of ten cases of hyperthyroidism, and in these ten cases the immediate clinical results were comparable to those which followed the removal of one lobe of the thyroid gland. The pulse-rate was lowered, the nervousness, sweating and weakness decreased, the lost weight was regained, the untouched thyroid gland diminished in size and grew firm in texture, as

after a successful ligation or a successful rest-cure. Of equal significance, although the operation was much more severe and of longer duration than a thyroidectomy, was the fact that there was but little postoperative reaction, that is, little so-called postoperative hyperthyroidism. But this, however, was not a remarkable effect, for according to the writer's point of view, part of the electric generative plant of the vegetative nervous system had been removed. The result of this procedure, however, was not as lasting as that of the removal of one lobe of the thyroid gland.

CONCLUSION

The evidence at hand is too meagre to be conclusive and is offered only as so much data in favor of the general thesis. Of the utmost interest is the fact that the symptoms of hyperthyroidism are so completely "adrenal" in nature,—the driven heart, the activated nerves, the increased metabolism, the sweating, the vasomotor instability, the dilated pupils, the increased pulse-pressure, all of these show a sensitization due to adrenalin. What is accomplished so strikingly by simply cutting off the sympathetic nerve-supply to the thyroid gland, may apparently be achieved on a much greater scale by the removal of one of the generators instead of by merely severing some of the feed wires.

The thyroid gland is governed, at least largely, by its innervation; the innervation is regulated largely by the adrenal glands; the adrenal glands are controlled by the brain and nerve-centres, though chemical activity probably also plays a rôle. The thyroid gland certainly cannot originate hyperplasia, the thyroid has hyperplasia imposed upon it; the adrenal glands cannot stimulate themselves, stimulation is imposed upon them; the nerve-receptors cannot engage in self-excitation, excitation is imposed upon them by the physical and chemical forces of the external and internal environment. The entire nerve-mechanism, the adrenal glands, the thyroid gland, and in a secondary sense other ductless glands, act reciprocally; that is, nerve-tissue, the adrenal glands, the thyroid tissue, all collaborate in a stepping-up process—a stepping-up of activity. In certain individuals, because of some previously existing unknown factor, some chemical or physical imbalance, the normal controls become inefficient or are lost; and a reciprocal excitation continues after the environmental excitation that initiated the activity, has ended.

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CHAPTER XXIX

THE RÔLE OF THE SYMPATHETIC NERVOUS SYSTEM IN PAINFUL AFFECTIONS OF THE FACE[1]

MAX MINOR PEET, M. D.

INTRODUCTION

INTEREST in the possible rôle of the sympathetic nervous system in the production or transmission of painful sensations in the face was aroused by the failure of therapeutic measures, directed against the trigeminal nerve, to afford relief in cases of so-called atypical neuralgia. This group is ill defined and undoubtedly includes painful conditions of diverse origin. It is also probable that the sensations of pain are transmitted over different nerves. The author has attempted in the following paper to indicate one type: those possibly of trigeminal tract origin, which may be separated from the group of atypical neuralgias.

The symptomatology of the so-called atypical neuralgias is characterized by its diversity, probably because it has not been possible to distinguish the various types. Certain characteristics, however, are common to the majority of cases. The pain is generally described as a dull, aching, burning, or pressure pain with exacerbations of greater intensity. Glaser (12) has compiled sixty-four descriptive adjectives used by one hundred and forty-three patients. In contradistinction to major trigeminal neuralgia, the pain in the atypical cases is seldom referred to the anatomical limits of any branch of the fifth nerve. In fact if a few cases are eliminated which the author is inclined to believe are of fifth-nerve origin although not related to trigeminal neuralgia, none of the so-called atypical neuralgic pains follow any known anatomical distributions. The temple, cheek, and the deep parts within the orbit, are the usual regions affected. The lower jaw may be involved, but less often than the upper. The pain frequently spreads to the posterior auricular and mastoid regions and

[1] From the Department of Surgery, University of Michigan.

in some patients to the neck and arm. It is always felt in the deeper tissues, never on the surface as in trigeminal neuralgia.

The pain is usually continuous for several hours, appearing in some cases at irregular intervals, in others with great regularity. In exceptional cases the pain may persist without intermission for months or years. It varies considerably in severity, and exacerbations of great intensity, especially when the patient is tired, nervous or excited, are the rule. No trigger zones exist, and no form of external stimulation has a bearing on the pain. Headaches, sometimes of the migraneous or hemicranial types, are rather frequently associated with the atypical neuralgias, but the two may not appear coincidentally and many patients are never so affected. Flushing of the face, lacrymation, and other phenomena suggestive of sympathetic origin are frequently noted.

The question arises as to whether these atypical neuralgias are of organic or of functional nature. The neurologist and psychiatrist generally consider them as of the latter, but the usual lines of treatment based on this conception have signally failed. A few probably belong in the group of neuroses, but some painful affections, long considered as belonging to this group, may in the light of recent work, be classified as of sympathetic origin. Of particular significance are the very suggestive results obtained by von Gaza (11) and repeated by Scrimger (21) and by Archibald (1), in cases of vague abdominal pains. These authors report relief of such pains by the section of certain thoracic white rami. If this work is substantiated it indicates that these pains are either of sympathetic origin or are transmitted over sensory fibers which are incorporated in the sympathetic white rami.

If all cases of atypical neuralgia cannot be considered as psychogenic in origin, then the pain is either of central type or due to some peripheral lesion. If the latter, the existence of some tangible course for the transmission of the painful sensation must be admitted. In the face there are anatomically only three possibilities,—the trigeminal, the facial, and the sensory fibers accompanying the sympathetic nerves. The location of the lesion is equally uncertain. However if peripheral, it is practically limited to a lesion in the Gasserian, geniculate or sympathetic ganglia, or to a disease of their branches. In addition, it is possible that the nodosum ganglion of the vagus sends some fibers to accompany the sympathetic ganglia.

The fifth nerve naturally attracted first attention, but with a clearer

conception of the symptomatology of trigeminal neuralgia the radical differences in the type of pain in typical and atypical neuralgias was recognized. In spite of these differences, several surgeons have sectioned the sensory root of the Gasserian ganglion in cases of atypical neuralgia, but with almost uniform failure to afford relief. The fact that in all known affections of the Gasserian ganglion or its branches, the pain is referred to the extreme distal distribution of the particular nerves involved, while in the usual atypical neuralgias such an anatomical limitation does not exist, proves quite conclusively that the fifth nerve plays no rôle in these atypical affections.

Occasionally a diagnosis of atypical neuralgia is made in which the pain actually follows completely the distribution of one or more branches of the Gasserian ganglion. It is this group that is considered of possible central trigeminal origin. The pain is deep seated, continuous, and is frequently described as a pressure pain, thus resembling the usual atypical case. It is believed to be of trigeminal origin because of its exact anatomical distribution. Relief has been afforded in some cases by deep alcohol injection. The following case history illustrates this type of neuralgia. The patient was first examined eighteen months ago.

REPORT OF CASES

Case 1. For seven years this patient, a woman, had had constant burning, pressing pains in the entire distribution of the maxillary branch on the left, and for six and one-half years a similar pain on the right. There were frequent exacerbations, characterized by great intensity of pain and a flushing of the face, but at no time had the pain entirely ceased. Bilateral alcohol injections were made at the foramen rotundum. Immediate anesthesia and complete relief from pain was obtained on the right, the relief continuing to date. Incomplete anesthesia, but temporary relief from pain was obtained on the left. After a few days, pain returned on this side. Intracranial section of the second division is now recommended.

Even though the atypical pain is confined to the distribution of the fifth nerve, relief may not be obtained by section of the sensory root of the Gasserian ganglion.

Case 2. The author performed this operation in March, 1923, upon a patient who complained of an intense, burning pain, of one year's duration, in the entire distribution of the second and third divisions of the left Gasserian ganglion. The pain was constantly present, with exacerbations, especially when the patient was tired. The atypical nature of the pain was recognized and the operation was performed reluctantly. For a few weeks he was free from pain; then it returned in

its original intensity. In February, 1925, the superior cervical sympathetic ganglion was excised and the adventitia stripped from the common, internal, and external carotid arteries without benefit. His pain is unchanged today, although he has tried numerous drugs and suggestive treatment.

The persistence of pain in this and similar cases after section of the sensory root of the Gasserian ganglion does not prove that it is not of trigeminal origin, but simply that these sensations are not transmitted through the ganglion and the sensory root. A similar persistence of pain sometimes follows section of the sensory root in cases of postherpetic trigeminal neuralgia (16). In fact, pain in the latter disease may closely resemble the particular type of atypical neuralgia under consideration. The persistence of postherpetic pain after section of the sensory root proves that pain of central origin can be referred to the periphery of the trigeminal division, even though the pathway for its transmission has been interrupted. Reasoning on analogous grounds, it appears probable that this particular type of atypical neuralgia is of trigeminal origin, the lesion being in the trigeminal tract in the medulla or pons.

According to Sluder (22) many atypical pains in the cheek, upper jaw, lower jaw, and retro-auricular regions are due to irritation of the sphenopalatine ganglion. Further work however has tended to disprove his assertions. Both Cushing (4) and Frazier (9, 10) have shown that excision of Meckel's ganglion, a more certain method than alcohol injections, fails to relieve these cases. The author does not deny the existence of the Sluder syndrome although he does not believe it to be of sphenopalatine ganglion origin. It should be considered as one type of atypical neuralgia, the origin of which is unknown.

The possible rôle of the facial nerve in atypical neuralgias is still uncertain. Hunt (13, 14) has shown that sensory fibers from the geniculate ganglion supply certain portions of the ear, and Ruskin (19, 20) has claimed an intra-oral distribution. The author has frequently stimulated the great superficial petrosal nerve, both by direct pressure before and after its division and by a weak electrical current. When the stimulus is applied to the proximal end the patient has invariably complained of severe pain deep within the ear and on one occasion pain was also referred to the back of the mouth. However, this induced pain does not resemble the type associated with the atypical neuralgia, a fact which in a way eliminates from consideration the great superficial petrosal nerve and its component

in the sphenopalatine ganglion. The facial nerve also carries deep pressure sensation from the entire face (5, 15). Since the discomfort in atypical neuralgia is commonly described as a pressure pain, the possibility that this sensation is transmitted over the facial nerve must be seriously considered. Proof will await the observation of a patient suffering with atypical neuralgia who subsequently develops a complete facial paralysis. Experimental, temporary paralysis by the injection of novocaine probably is of little value, since the injection must be extracranial. It is possible that pressure-pain sensations may be transmitted along the fibers carrying muscle-sense, which pass centrally along the motor root. At present, evidence that a lesion in the facial nerve can produce the pain of atypical neuralgia, or that the painful sensation may be transmitted over this nerve, is entirely lacking.

There remains, by the process of exclusion, only the sympathetic nervous system as a possible source of painful affections of the face. The function of the sympathetic nervous system, according to the present conception, is entirely the transmission of efferent nerve-impulses. Accepting this view, the sympathetic nerves may produce pain by vasomotor spasm, but the recognition of such painful sensations must be transmitted to the brain over other nerves. These must be at least grossly associated with the sympathetic fibers, otherwise it must be assumed that the afferent impulse passes over the trigeminal or facial nerve.

It is well known that sensory fibers from the spinal nerves accompany and in many instances are incorporated in the sympathetic nerves in other parts of the body. In fact some sympathetic nerves, like the great splanchnic, contain a large number of fibers from the thoracic posterior root ganglia. No fibers positively identified as sensory have been found passing to the superior cervical sympathetic ganglion, but there are numerous branches from this ganglion which pass to the glossopharyngeal, vagus and hypoglossal and to certain sensory branches from the vagus and upper cervical nerves. It is possible that these sensory fibers accompany the sympathetic nerves in the head as they do in other regions.

The group of nerve-fibers (labeled 2, in Fig. 149) passing between the nodosum ganglion of the vagus and the superior cervical sympathetic ganglion are of special interest. Whether these fibers are of sympathetic or of vagus origin has not been determined. Degeneration

experiments will be made to decide this point. At present it is possible only to theorize regarding these fibers, but certain data already accumulated suggest their sensory nature. In one patient

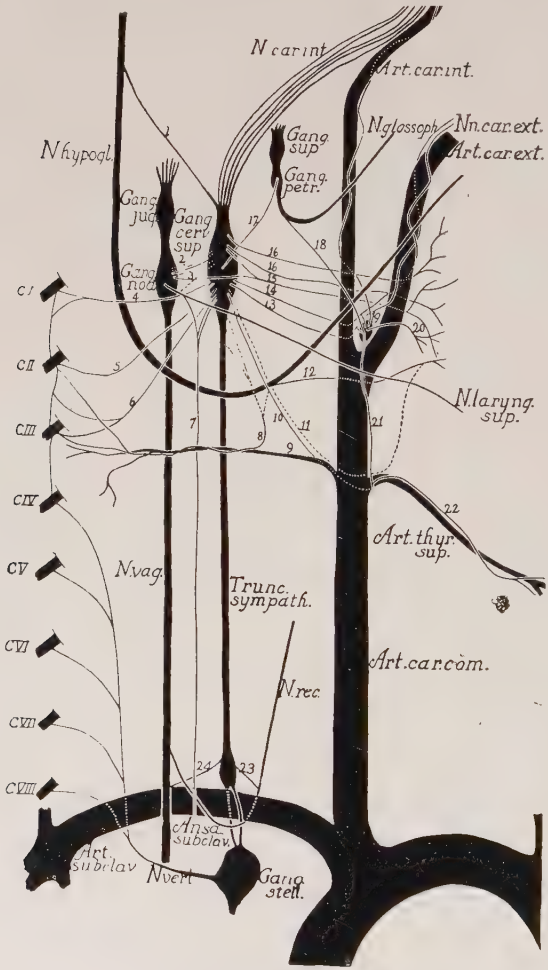

FIG. 149. Diagrammatic representation of the cervical sympathetic trunk and of the branches of the superior cervical sympathetic ganglion in the cat: 1, branch to hypoglossal nerve; 2, fibers connecting superior sympathetic ganglion and the nodosum ganglion of the vagus; 3, fiber from vagus to a branch of sympathetic; 4, 5, 6, gray rami to cervical nerves; 7, gray ramus to a branch of common carotid. (From Billingsley and Ranson (3), p. 370.)

suffering from severe, constant pain in the cheek just below the zygoma, electrical stimulation and pinching of these fibers aggravated the pain. It immediately stopped on cutting the fibers. This patient had had atypical neuralgia intermittently for several years, but for the past six months it had been constantly present, although varying much in intensity. Although at the time of operation it was comparatively mild, stimulation of the fibers between the vagus and sympathetic ganglia increased its intensity to the maximum suffered previously. This induced pain was in the same location and of the same quality as the atypical neuralgia. Whether this pain should be considered as of sympathetic or vagus origin is not certain because the course of the fibers stimulated, is not known. If they are of vagus origin they must ascend with branches from the superior sympathetic ganglion, since Ranson and Billingsley (17, 18) have shown that there are no descending fibers in the cervical sympathetic trunk. These authors (2, 3) have also shown that there are no preganglionic fibers in the branches of the superior sympathetic ganglion. It must, therefore, be assumed that the fibers between the nodosum and sympathetic ganglia are either gray rami from the latter, or are sensory fibers from the vagus, which simply pass to the sympathetic ganglion on their course to the head. In other words, the connection is only a gross anatomical one.

Thus far the sympathetic nervous system has been considered in relation to atypical neuralgias only as regards its gross anatomical structure, ignoring the fact that the chance inclusion of sensory fibers from other nerves actually has no bearing on the function of the sympathetic nerves and therefore no relation to the possible sympathetic origin of atypical neuralgias.

Considered from the modern neuro-anatomical standpoint, i.e., that the sympathetic nerves carry only efferent impulses, the sympathetic nervous system can only play a rôle in the atypical neuralgias of the face if such neuralgias are due to vasomotor spasm.

Sympathetic innervation of the external and internal carotid arteries, including the branches of the latter in the brain, has been definitely established. There is also considerable clinical material indicating the occurrence of spasms of these vessels. The missing link needed to complete the chain of evidence implicating the sympathetic nervous system in the atypical neuralgias is proof that such spasms cause pain of a similar nature. Such proof is not entirely

lacking. The well-known pain due to vascular spasm in the extremities resembles in many cases the pain of atypical neuralgia in the face.

In some patients, Frazier (7) has shown that electrical stimulation of the superior cervical sympathetic ganglion produces pain in the zone of the trigeminal distribution. The author has confirmed this observation in a number of patients. The similarity between this induced pain and that of atypical neuralgia was demonstrated in the same case, previously mentioned (pp. 638-639). This patient in addition to the subzygomatic neuralgia, complained of a different type of pain in the region corresponding roughly to the temporal muscle. This pain fluctuated in intensity and had been present much of the time for several months. Section of the nerves between the nodosum and superior sympathetic ganglia stopped the pain in the cheek but the temporal pain persisted. Under local anesthesia the superior cervical sympathetic ganglion was stimulated electrically and the pain in the temple was immediately aggravated. Similar stimulation of the internal carotid branches from the superior sympathetic ganglion increased the severity of the pain to a degree which he considered unbearable. This induced pain was exactly similar in location, type, and intensity to the severe exacerbation. The pain immediately ceased on dividing the carotid sympathetic branches.

The occurrence in this patient of two distinct types of pain in two locations is not unusual. The interest lies in the accentuation of the pain, in the cheek by stimulation of the fibers between the nodosum and the superior cervical sympathetic ganglia, and in the temporal region by stimulation of the carotid plexus. It suggests that the difference in the pain in the two locations was due to a difference in etiology or transmission. Both types of pain were relieved by section of the nerves apparently involved.

Further suggestive evidence is furnished by the induction of, or increase in severity of, the neuralgic attacks when the patient is fatigued and especially when worried, frightened or angered, i.e., subject to emotions which are known to stimulate the sympathetic nervous system.

Dr. Temple Fay has called the author's attention to an interesting sign presented by some cases of atypical neuralgia. He found that irritation of the carotid and often of the temporal and occipital arteries by pressure, produced pain in the regions supplied by them.

The artery was often sensitive to pressure. Similar irritation on

the opposite side produced no symptoms. The interpretation of this observation is not clear, but it suggests a vasomotor irritability, possibly on a sympathetic basis.

Section of the various branches of the superior cervical sympathetic ganglion has not been performed in a sufficient number of cases of atypical neuralgia to warrant drawing conclusions from the clinical data available. Frazier (6–8) has reported ten cases, with favorable results in only one, and the ultimate outcome of this case is unknown. It is probable that the majority of these cases should be classed as paresthesias, probably of central trigeminal origin, and should not be included with the atypical neuralgias. The author certainly would not have expected relief from section of the sympathetic nerves in most of those reported. His own experience is also too limited to draw definite conclusions. However, the evidence so far accumulated suggests that the sympathetic nervous system, through vasomotor spasms does play a rôle in the etiology of some cases of atypical neuralgia. The chief difficulty at present lies in the inability to differentiate the various diseases now grouped under this term. When such differentiation has been made, it will be possible to select the cases more intelligently and to decide upon their suitability for operation on the sympathetic nerve. A sufficient number of cases representing a single type of atypical neuralgia will then be available and definite conclusions can be drawn.

SUMMARY

1. The term atypical neuralgia is unsatisfactory for two reasons: first, the pains are not neuralgic in character; second, a number of unrelated conditions are probably grouped under one designation.

2. Unless of central origin, pain referred to the face must involve one of three nerves,—trigeminal, facial or sympathetic.

3. The peripheral trigeminal tract has been eliminated from consideration by the persistence of atypical neuralgic pain after section of the sensory root of the Gasserian ganglion.

4. One type of so-called atypical neuralgia should be considered of central origin, the lesion probably being located in the trigeminal tract in the medulla or pons.

5. Sensory fibers from various nerves, especially the vagus, may be incorporated in certain sympathetic nerves, although proof of

such association is lacking. If found, it will furnish an explanation for the transmission of painful sensations from the blood-vessels. Only in this gross anatomical sense can the sympathetic system be considered sensory.

6. Atypical neuralgic pain can be of sympathetic origin only if such pain is due to vasomotor spasm, since this system carries only efferent impulses. Certain observations, while not conclusive, suggest that some types of atypical neuralgia are of this origin. Somewhat similar pains, namely those of vascular disease of the extremities, are certainly of sympathetic origin. The reception of the painful sensation must however be transmitted over sensory nerves.

DISCUSSION

The following question submitted to Dr. Peet before the Commission, together with the answer to it, is here reported verbatim.

Dr. Timme: Are there any questions on Dr. Peet's presentation?

Dr. Fay: The points that Dr. Peet has brought up regarding this mechanism bring to mind a question that has arisen in my work so that I should like to ask him whether, in ruling out the other possible paths of entry for pain-sense into the brain, such as through the fifth, the ninth, the upper cervical posterior roots (which I have demonstrated), we may not associate the mechanism with the vagus. Furthermore, in attempting to locate this mechanism, may we not conclude that these fibers for pain are in reality sensory arcs (similar to the spinal mechanism) given off along with sympathetic fibers, although not of the sympathetic system, passing through the superior ganglia, not stopping there, but added to the vascular supply that goes forward on the chorioid arteries supplying the deep vascular structures of the head and brain?

Dr. Peet: I believe these are sensory fibers which by chance, we might say, accompany the sympathetic, passing along the sympathetic nerves, but not, in a functional sense, belonging to them. They certainly do not come from a lower level. After division of the trunk below the superior sympathetic ganglion, no degeneration is found in the superior ganglion; therefore any afferent connections to the brain must come in from either the vagus or the upper cervical nerves. I do not know whether the seventh and the ninth nerves play a part.

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CHAPTER XXX

DIENCEPHALIC AUTONOMIC EPILEPSY[1]

WILDER PENFIELD, M.D.

UNLIKE the cerebrospinal nervous system with its obvious and indispensable functions, the vegetative nervous system has been slow to come into its own. Only recently has its representation in the spinal cord and medulla oblongata been recognized, and still more recently its important representation in the midbrain and hypothalamus. The case to be presented would suggest that there are higher structures analogous to the cerebral motor cortex which are capable of producing, when irritated, paroxysmal motor discharges through the vegetative nervous system, similar to the focal discharges through the cerebrospinal system first described by Hughlings Jackson (2, 3) as epileptic.

REPORT OF CASE

J. H., aged forty-one, entered the Presbyterian Hospital, New York City, January 2, 1928, having been referred to the author by Dr. T. B. Protzman of Englewood, New Jersey. She gave the following history:

Past history. Previous illnesses: Operation ten years previously for suspension of the uterus and appendectomy. One year later exploratory laporotomy with removal of part of the left ovary because of adhesions. At five years of age the patient had fallen backward from a 7-foot wall landing on her back and striking the back of her head on the concrete walk. She was unconscious for two hours. It is understood that blood came from her nose and ears. After she regained consciousness she was up and about. *Eyes.*—She had worn glasses for reading but had no visual difficulty; no diplopia. *Ears.*—For the past eight years she had had gradual loss of hearing. The right ear was worse than the left. *Nose.*—No obstruction. No colds. *Throat.*—Negative. *Mouth.*—All of her teeth had been removed five years previously during an attack of headache on the supposition that this would cure her condition. *Cardiac and respiratory.*—Negative. *Gastro-intestinal.*—She had a considerable amount of abdominal distention. She was often constipated. *Genito-urinary.*—Nocturia two to three times. *Menstruation.*—Regular until recently. Two normal children. No miscarriages. *Weight.*—Always thin, had gained a little previous to present illness. *Disposition.*—Always excellent.

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[1] From the Surgical Service, Columbia University, and the Laboratory of Neurocytology, Presbyterian Hospital, New York.

Family history. Two brothers were deaf; nothing else of importance.

Present illness. The patient had had headaches ever since the accident to her head, at the age of five years. These headaches were occipital and had been severe for at least twenty years. The headaches occurred several times a week at first, but later they varied between several times a day and once a month. When the headache was severe enough, she had a "spell," became dizzy and felt that she might fall. Thirteen years previously, while sitting at the table, she suddenly cried out, "stiffened and fell under the table." She was unconscious for several hours and was thought to have had a convulsion which affected the arms, legs and neck.

Five years previously there had been a severe "attack of headache," and while "in coma" all her teeth were removed in the forlorn hope of reviving her. During this attack there were periodically recurring alterations in her condition, evidently identical with the seizures to be described. Nine days before admission, she had the most severe attack of all. During the six days of its duration she again showed the recurring seizures.

The headaches had often come on very suddenly following some movement, and sometimes were relieved just as suddenly as the result of some change of position, such as turning the head to the opposite side. She was always perfectly clear mentally, and showed a fortitude throughout which commanded the admiration of her friends and family.

Physical examination. The important findings were as follows: *Cranial nerves.*—1. There was absence of smell in both nostrils. 2. The optic disc margins were blurred especially on the nasal side and there was early papilledema. The retinal veins were fuller than normal. The visual fields were complete and there was no enlargement of the blind-spot. 3, 4, 6. The pupils were equal, but there was some irregularity of the left pupil. 5. The corneal reflexes were present, but sluggish. 7. Hearing was diminished in both ears; bone conduction was louder than air conduction. *Reflexes.*—The deep reflexes were present throughout and equal on both sides. They were all unusually active, particularly in the lower extremities. The superficial reflexes were always found to be normal except on two occasions when examination showed that the left upper abdominal reflex was absent, while the left lower and right abdominal reflexes were present. There was a slight degree of exopthalmos. The fingers showed tremor when extended, and the feet were somewhat tremulous.

Special examination. Roentgenography of the *skull*, January 10, 1928. The report of Dr. Ross Golden was as follows: "Stereoscopic films of the skull in the right lateral position show the floor of the sella to be intact, although apparently thin and not depressed into the sphenoidal sinus. The dorsum sellae is somewhat thin. The posterior clinoids cannot be seen. Films of the skull in the Grainger position show fairly well the greater part of the so-called Grainger line, which is the floor of the sella. It is non-recurrent, though thin. This evidence is very much against the evidence of a pituitary tumor. This suggests rather that the erosion of the posterior clinoids is the result of pressure from above and probably behind." Examination of the *blood* showed 3,680,000 red cells; otherwise the blood was normal. A Wassermann test of the blood and spinal fluid was negative. The

temperature varied from 98.6°F. in the afternoon to 100°F. in the morning. The pulse rate on an average was rather fast, 80 to 100. The respirations rate was 20.

Course. A ventriculogram was done under local anesthesia and air introduced directly into the ventricle through one occipital lobe. The fluid was clear, the pressure 250 mm. of water after about 10 cc. had been lost. Respiratory and cardiac oscillations in the fluid were very marked. 90 cc. of fluid were replaced by air without discomfort. The ventriculogram showed enormous symmetrical dilatation of the lateral ventricles (Fig. 150). In this figure the convolutional atrophy

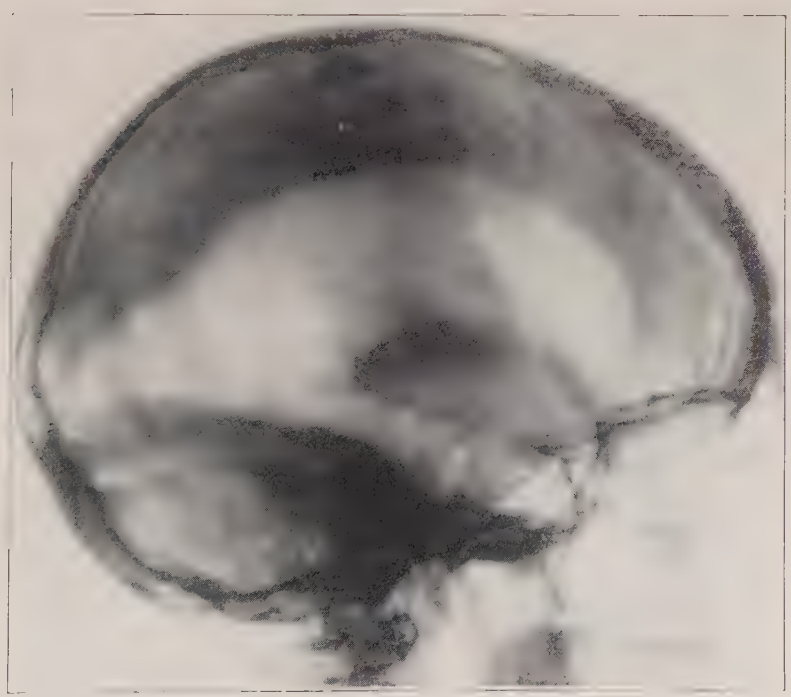

Fig. 150. Enlargement of the lateral ventricle shown by ventriculography. Note the convolutional atrophy.

of the skull due to the long continued intracranial pressure was also evident. In the lateral plate taken with the brow down, the posterior horns were shown (Fig. 151), but there was also a third shadow[2] situated above the tentorium over the roof of

[2] The location of this cavity was verified by autopsy; it was shown to communicate with the lateral ventricles of both sides through a defect in the tela chorioidea below the splenium of the corpus callosum. The author has seen such a cavity

the midbrain and between the occipital lobes of the cerebral hemispheres. The third ventricle was not shown in any of the plates, and the conclusion from the plates alone was block in the third ventricle.

Headaches. On the day following admission she stated she was lying in bed with her head on the left side. She was straining to void when suddenly she felt a sharp pain which extended from the lower occipital region along the midline. She "wriggled" her head about to the other side to change the position in the hope of stopping the pain. She felt stifled and had profuse diaphoresis. All symptoms

Fig. 151. Roentgenogram taken with brow down. Note the presence of air in the posterior horns of both lateral ventricles, also in the midline cavity over the roof of the midbrain. The posterior clinoids have been absorbed.

disappeared after voiding. Her hands trembled for a time following the attack. Except for this attack there were only occasional headaches during the first days in the hospital, and these were not increased by a ventriculography.

A *diagnosis* of tumor in the third ventricle was made, but operation was delayed for a few days.

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associated with internal hydrocephalus in four other cases, one of them verified by autopsy.

So far as he is aware the recurrence of this collection of fluid has not been previously pointed out. Although the cavity is surrounded by arachnoidea it is outside the subarachnoid space.

Beginning on January 11, the fifth day after the air injection, she had a headache and vomited. After twenty-four hours, it developed into a "headache attack" which, according to the patient and to her husband, was identical with the attacks from which she had suffered periodically for years.

On January 12, while suffering from the headache, she was given an enema. Regarding the procedure the nurse reported as follows: "She suddenly became flushed and had profuse diaphoresis. Pulse 126, rather irregular but of good quality." Following this attack the author saw her, and the pulse was then quite irregular and weak. Her face was pale. She was not perspiring. Hoping to dislodge the tumor from an unfavorable position, the author moved her head, turning the face down. She then suddenly flushed down to her breasts. There was no flushing of the feet but she perspired profusely and suddenly over the whole body. The pupils were small and equal and reacted to light both directly and consensually. The deep and superficial reflexes were about the same as before the attack, the abdominal reflexes being present, and the plantar responses indeterminate. There was transient ankle clonus.

From that time on the headache was apparently continuous. The patient lay most of the time without moving, in obvious pain. She would answer questions briefly but clearly. At recurring intervals she had an attack in which the same phenomena reappeared regularly. The attack was explosive and heralded by prodromal symptoms and the phenomena followed a fixed order just as may happen in a series of epileptic convulsions or status epilepticus. The amazing feature of each seizure was that the succeeding motor phenomena were confined to the structures controlled by the vegetative nervous system.

Description of attacks. A typical attack may be described as follows: The patient stirred and asked for cracked ice. Then her face and arms flushed a deep red. She lay quietly and respirations became very slow. Tears rolled from both eyes and fell upon the pillow. She broke into a profuse diaphoresis over the entire body. Saliva ran out of the corner of her mouth. The eyes were open, the pupils were large and the eyes protruded.[3]

The pulse was strong and rapid. Gradually the flushing faded, the pulse became weak and slow. The patient then hiccoughed from three to five times, and this was followed shortly by transient shivering. The respirations became Cheyne-Stokes in type. The patient could be roused to questions throughout the attack, but she would answer little.

Late on the night of January 12, the attacks became more severe. At such times the patient was unconscious. The duration of each attack was from five to twelve minutes, and several of them were followed by shivering of five minutes' duration. The temperature fell to 97°F. During one attack she was incontinent. Occasionally there was a shivering or a hiccoughing without an attack, and occasionally tears and diaphoresis did not follow the flushing. During one of the more severe attacks the respirations became much slower and stopped for a brief period. She was seen by Dr. William V. Cone, who punctured the lateral ventricle through one of the trephine openings made for the ventriculography. There was a sudden escape of air and fluid under such high pressure that a bit of cerebral tissue was

[3] Protrusion of the eyes was not invariably present.

blown through the brain-needle onto his cravat. Following the puncture she regained consciousness.

A few hours later in an unusually severe attack respirations practically failed and he punctured the other ventricle, again removing air and fluid under much increased pressure. At the time of this puncture she seemed unconscious, but immediately following it she said she felt better. She shivered violently then for about five minutes.

After these attacks had continued at recurring intervals for about twelve hours, it was recognized that although the motor discharges were confined to the autonomic nervous system, the association of the phenomena with a tumor of the third ventricle made it evident that the condition was analagous to status epilepticus. Consequently, sodium bromide was administered and was followed by steady improvement in the patient's condition. Either *post hoc* or *propter hoc*, the attacks became much less severe and less frequent and the patient began to talk and eat. She had been able to eat a little, however, even between severe attacks and did not vomit during them. For a time a few hiccoughs followed whenever she drank anything. She had been unable to void to command while the headache lasted and she could now do so only on getting out of bed.

On January 16, her condition seemed to be quite satisfactory, although she was having trouble as usual with constipation and inability to void. It was therefore determined to proceed with a craniotomy and removal of the tumor of the third ventricle through the lateral ventricle on the following day. While blood was being taken for examination that evening, she suddenly flushed and seemed to have air-hunger, but none of the other characteristics of an attack. She had a few attacks during the night.

At 5:00 a.m., just four hours before the scheduled operation, she had a severe attack. Respirations stopped for about five minutes. Artificial respiration brought her back and she seemed to be rallying when there was another sudden change, perhaps a second attack, and she died at 5:30 a.m. The notes of the patient's nurse are remarkably vivid and accurate.[4] They are therefore added here without alteration.

January 13, 1928: 7:20 a.m.: Attack characterized by previous symptoms. Cheyne-Stokes breathing preceded attack for 4 minutes, approximately. Flushed face. Profuse diaphoresis and slow, labored breathing, lasting 10 minutes. Unconscious for 15 minutes. Cheyne-Stokes breathing followed attack and lasted for 8 minutes. Patient invariably asks for ice just before attack. Patient comfortable. No headache. Cold only complaint.

8:15 a.m.: Attack lasting 10 minutes. Face flushed. Profuse diaphoresis. Breathing rapid at onset (30) becoming Cheyne-Stokes in character. Slowest rate 6. Pulse 100 and full at onset, becoming weaker and slower. Eyes fixed at onset. Attack followed by severe shaking chill lasting 5 minutes. Temperature 100. Salivation present during attack. Tears came from both eyes slowly.

9:00 a.m.: Attack. Much like last one. Tears and salivation both present. Flush and diaphoresis. Duration 12 minutes. Unconscious.

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[4] The accurate records of Miss Hilda Minshall have contributed largely to the value of these observations and indicate the high level of nursing efficiency in the Presbyterian Hospital Training School.

9:35 a.m.: Attack lasting 5 minutes. Tears, slight salivation. Flush, diaphoresis, unconscious. Eyes open, prominent and fixed, at onset. Followed by two attacks of shivering about 4 minutes after end of attack. Incontinent.

10:07 a.m.: Attack lasting 4 minutes. Unconscious for approximately 10 minutes. Tears. No salivation apparent. Pulse weaker. Respiration, 4. Flush present but not at onset. Shivering at 7-minute intervals for approximately 4 seconds, three times. Patient has been conscious and quieter. Breathing more easily and regularly than at any time since turned on back. Now on right side and apparently comfortable.

11:02 a.m.: Attack lasting 4 minutes, approximately. Slight. 1st, changed respirations, labored 6–4. 2nd, flush, not very pronounced. 3rd, slight salivation. Respiration, Cheyne-Stokes, but easier at 11:05. Tears at 11:05. No apparent loss of consciousness. Followed by 3-second attack of goose-flesh, shivering and hiccoughs. Says she wants to sleep. Slept from 11:20 to 12:15, quietly.

12:15 p.m.: Attack lasting 9 minutes. 1st, asked for ice. 2nd, face became flushed. Respiration labored and irregular (4–5 a minute). 3rd, diaphoresis. 4th, tears and salivation. Unconscious from onset till 12:25.

1:25 p.m.: Attack lasting 12 minutes. 1st, deep sighing respirations. 2nd, flush. 3rd, loss of consciousness. No salivation or tears. Conscious at 1:37, but respirations irregular till 1:45. Attack of hiccoughs at 1:45. Lasted only about 30 seconds. No shivering.

2:05 p.m.: Short attack. 1st, restless, moving of hands and feet. 2nd, flushing of face. 3rd, change in respirations. Tears, salivation and loss of consciousness. Regained consciousness before flush disappeared. Patient dozes most of the time between attacks, but is perfectly clear mentally when addressed and is very co-operative. Says her head aches "off and on."

3:30 p.m.: Attack lasting about 5 minutes. 1st, restlessness. 2nd, convulsive breathing. 3rd, flushed face, tears and salivation. This came on almost immediately after moving patient from one side to the other. Pulse did not go to pieces quite so much as usual. Hiccoughed 4 times after attack. After attack, but while she still had Cheyne-Stokes breathing, it was noticed that goose-flesh appeared on her fore-arms while breathing, and disappeared in each interval between breathing spells.

5:02 p.m.: 1st, restlessness. 2nd, flush. 3rd, convulsive respirations. 4th, diaphoresis. No tears or salivation. Duration 6 minutes. Hiccoughed 3 times, 5 minutes after. Pulse not as good quality since 4:00 p.m. Hiccoughed 5 times at 6:15 p.m.

6:40 p.m.: 1st, restlessness. 2nd, flush, convulsive breathing. 3rd, loss of consciousness. 4th, diaphoresis. Patient was conscious during first few seconds of attack. Tears and salivation both present. Hiccoughed 3 times and moved legs convulsively after attack but did not shiver then. Duration 5 minutes. Pulse, 96. Respiration, 6. Just before attack patient had taken 2 ozs. of oatmeal gruel and said that it was good. Shivered 5 minutes after attack was over, twice for 30 seconds with a 60-second interval; hiccoughed twice at 6:55 p.m. Quiet and dozing.

7:30 p.m.: Hiccoughed 4 times. Face flushed, slight diaphoresis on face 30 seconds. Conscious and says she is comfortable. Respirations of slight Cheyne-Stokes character continue.

8:15 p.m.: Hiccoughed 3 times. Slept for ½ hour.

10:10 p.m.: Hiccoughed 4 times.

10:15 p.m.: Face and arms flushed, shivering. Slight tremor over body. Convulsive respirations for 60 seconds, salivation. Pulse, 96. Respiration, 8. Diaphoresis. Eyes fixed and staring, with apparent loss of consciousness for 60 seconds of convulsive respirations. Mucus in throat since attack. Asks to have the light put out and not to be disturbed, as she wants to sleep. Slept from10:30–11:00 p.m. Respiration, 16, deep and regular. Pulse at 11:00 p.m. somewhat thready—104. Hiccoughed 6 times at 11:00 p.m. and 4 times at 11:20 p.m. Dozing again. Conscious when roused. Respirations irregular—Cheyne-Stokes. No headache—no pain. Wonders what gives her hiccoughs. Does not like being disturbed every little while. Dozing and quiet from midnight until about 5: a.m. Restless and wakeful between 5 and 6 a.m. No attacks after 10:15 p.m. Conscious when roused. No headache. Hiccoughing at intervals, not continuous.

1:00 a.m.—6 times.
1:45 —8 times.
2:20 —6 times.
4:00 —8 times.
5:00 —3 times.
5:15 —6 times.
5:45 —4 times.

Resting and sleeping between 6 and 7 a.m. Respirations through night varied and irregular for the greater part of the night resembling Cheyne-Stokes at times.

January 14: Frequently 6 breaths for ¼ minute; 0 for 2nd ¼ minute; 6 for 3rd ¼ minute; 0 for 4th ¼ minute. Varying in quality—sighing or puffing expiration. Respirations quiet and regular between 6 and 7 a.m. No diaphoresis except slight, in attack at 7:30 and 10:00 p.m. Has not voided through the night. Sleeping very quietly with regular respirations from 7:15 to 8:40. Pulse fair, quality regular, rate about 90–80.

Hiccoughed:
8:40 a.m.—2 times.
8:48 —4 times.
8:57 —5 times.
9:17 —4 times.
9:45 —4 times.

Is thirsty and sleepy, wants to be let alone. Complains of pain in bladder. Lower abdomen quite distended. Unable to void naturally even though sitting up. Asked to be catheterized. Poultice to lower abdomen, but no effect. Tried again to void sitting on edge of bed, but without success.

Hiccoughed:
10:25 a.m.—2 times.
10:45 —2 times.
10:50 —4 times.
10:55 —2 times.
11:00 —3 times.
11:10 —4 times.

Always hiccoughs 3–4 times after drinking. Appetite very poor. Voided naturally sitting on commode 525 cc. Somewhat bothered by gas. Bowels

moved (liquid small amount) at 2:00 p.m. Hiccoughed 10 times after drinking at 2:15 p.m. Mentally clearer than at any time. Says she "feels much better."

2:00 p.m.: Sleeping quietly and breathing naturally for long periods. Shivered for 30 seconds, but no other change.

Hiccoughed:

1:00 p.m.	—3 times.
2:05	—4 times.
3:10	—5 times.
3:55	—2 times.
4:15	—9 times.
4:55	—2 times.
5:40	—3 times.
6:15	—5 times.

Awake, quiet and comfortable during evening. Pulse, 90; respiration, 16, regular.

January 15: 9:00 a.m.: Hiccoughed twice after drinking at 9:00 a.m. Took a few teaspoonfuls of coffee and half a grape fruit for breakfast. A few eructations of gas this a.m. No discomfort, no headache. Comfortable, taking fluids well.

Hiccoughed:

10:25 a.m.	—3 times.
11:20	—once.
12:00	—twice.
2:00	—3 times.
4:15	—twice.

5:00 p.m.: Quiet comfortable day. No attacks. No pain. Bright and cheerful. Appetite slightly improved, but still very poor. Takes fluids well, however.

January 16: 7:30 a.m.: Comfortable this a.m. except for feeling of "pressure" in lower back of head. This has increased in severity until very troublesome by 1 p.m. No relief obtained from medications. Unable to void this a.m.

10:00 p.m.: Slight attack. Flush on face—4 sighing respirations. Eyes fixed for an instant. Slight diaphoresis on face. Conscious and says she is comfortable. Pulse, 72. Respiration, 12. Temperature, 97.4°F. Extremities warm. Quiet and sleeping again. Respirations regular.

11:00 p.m.: Complained of "head aching quite badly." Took bromide 1 gm. and drank 100 cc. water.

January 17: 1:00 a.m.: Attack lasting 5 minutes. Complained of headache—restlessness. Flush over face and arms. Convulsive respirations and heavy sighing. Eyes fixed and staring widely, tears and salivation. Saliva slightly frothy. Loss of consciousness through the attack. Respirations, 7, and later, 12—irregular. 1 long sighing and 1 short, alternating. Conscious after attack, but rather sluggish. Asked for ice, but took fluid grudgingly—said she wanted to sleep. Slept quietly—respirations becoming regular. Hiccoughed once.

2:30 a.m.: Attack 3 minutes. Said she felt warm. Face and arms flushed—asked to be sponged off, and for a piece of ice. Convulsive respirations, 5 per minute, regular. Eyes staring, tears, salivation. Loss of consciousness. Diaphoresis over face and arms. Respirations somewhat stertorous but regular and rising to 7 and 9.

2:45 a.m.: Attack 3 minutes. Face and arms flushed. Convulsive respirations, 5, regular, stertorous, eyes staring. Tears, salivation, unconsciousness through attack. Saliva frothy. Respirations irregular, rate 5–10. Patient holding breath for 30 seconds, and 5 or 6 for the second 30 seconds, alternating with regular respirations at 10 or 12 for each 60 seconds. Conscious but sluggish. Said her head felt better. Took a little broth and cracked ice. Respirations continued irregular. After pause of 15–20 seconds respiration is resumed at rate of 10–12 per minute. Diaphoresis over entire body.

3:00 a.m.: Sodium bromide given. Cessation of respiration for about 2 minutes. Artificial respiration resorted to with success. Started breathing again and spoke, Convulsive attack followed by stertorous breathing and cyanosis of face. Eyes fixed and staring, slight froth in mouth. Pulmotor used without effect and breathing ceased. Pulse regular and fair through the night (becoming thready during attacks) and ceased at 5:30 a.m., after respirations stopped.

Autopsy

Thanks to the invariable courtesy of the Pathological Department, the author was enabled to perform the autopsy himself, three hours after death.

Gross examination.—Scalp.—The hair was normal in distribution. Two healed incisions were present over the occipital pole. The skull was normal in size, shape and thickness. There was some convolutional marking on its under surface. *Dura mater.*—The dura mater was thinned. It seemed to be under considerable tension. There were rather marked small herniations in the temporal fossa, such as are often associated with increased intracranial pressure. There were no particular adhesions to the arachnoid. The sinuses appeared normal. *Leptomeninges.*—The pia-arachnoid appeared normal in color. There were no opacities, and there was no evidence of exudation. Cerebrospinal fluid spaces at the base of the brain were full and not collapsed. This was also true of the peribulbar and interpeduncular spaces. The cisterna magna was obliterated by marked herniation of the cerebellum. The intergyral fissures were practically obliterated, due to convolutional flattening. *Pial veins.*—There was marked congestion of the brain itself. However, this was noted only of the brain and the cerebellum, the pons being pale, as described later. *Brain.*—The brain weighed 1,500 gm. It was rather red in appearance, and of normal consistency. The hemispheres showed great convolutional flattening.

The medulla and pons were strikingly white and only the larger pial vessels were here visible. In contrast with this, the cerebrum and cerebellum were unusually red and suffused, many small pial vessels being visible (Fig. 152).

The lateral ventricles were greatly dilated, but the fourth ventricle was of normal size. The third ventricle was not dilated; but in its anterosuperior portion, protruding into the foramina of Monro on each side and pushing the overlying fornix upward, was to be seen a round, pearly white tumor (Fig. 153). It was covered with a loose capsule formed by a sheet of tissue, which was continuous with the chorioid plexus as it appeared in the foramina of Monro. When this capsule was opened the tumor fell out, round like a marble and with no attachment. Although the situation of the neoplasm was within the third ventricle, it pushed the pillars of the fornix upward and thus pressed upon the mesial anterior and superior aspect of the thalamus on each side.

The posterior end of the corpus callosum was raised, and a defect through it caused a communication to exist between the lateral ventricle on each side and a cystic cavity bounded above by the cerebral hemispheres, posteriorly by the cerebellum and below by the roof of the midbrain.

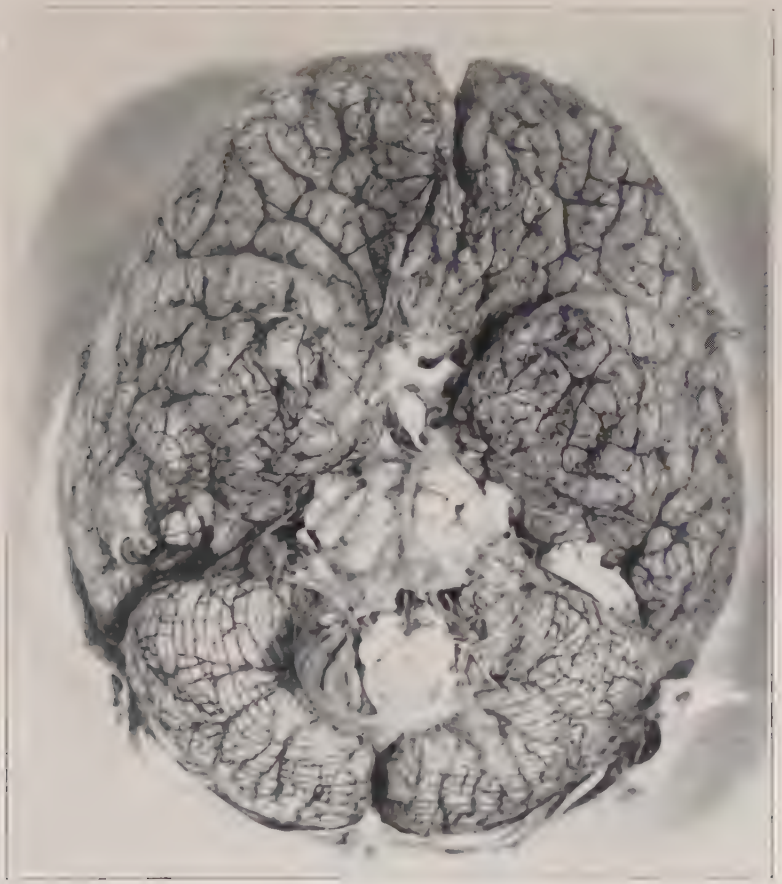

FIG. 152. Photograph taken immediately after the necropsy and before fixation. The pallor of the brain-stem is in striking contrast to the unusual suffusion of the rest of the brain.

The retinae show a swelling of the nerve-head with exudation of lymph, most marked about the disc, but also seen along the retinal vessels (Fig. 154).

Microscopic examination.—Examination of the thalamus showed that the nerve-cells and neurofibrils were normal throughout. Neuroglial astrocytes and oligo-

dendroglia were also normally preserved, and showed no abnormal reactions. There was perhaps some increase in the number of oligodendroglial cells of the white tracts

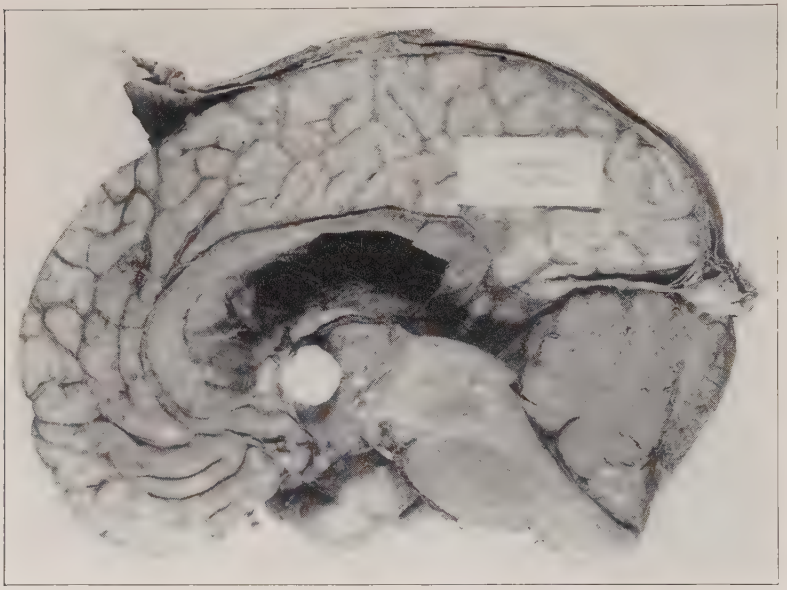

Fig. 153. Longitudinal section of brain, after fixation, showing cavity over the midbrain connecting with the lateral ventricle, with a "pearly tumor" present in the foramen of Monro covered by the arching band of fornix.

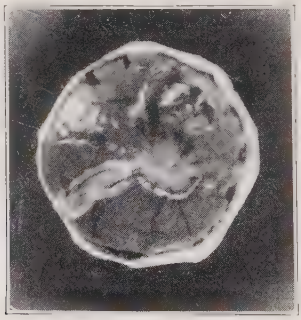

Fig. 154. Excised retina, showing early edema of the nerve-head and patches of exudate.

beyond the normal number. In the brain-stem the nerve-cells seemed to be normal, as shown with toluidine-blue. The blood-vessels here contained no corpuscles.

In the area beneath the ependyma, where the tumor impinged and where edema and cavitation were seen grossly, there was a fading out of cell-structure. The neurofibrils did not stain with silver and the astrocytes were not impregnated by gold-chloride. The tissues were separated by fluid. There was, however, no evidence of reaction—no gliosis, no fat-laden cells, but there seemed to be some increase in the number of local blood-vessels.

Finally, these areas just mentioned were evidently produced by acute edema, being the immediate effect of the pressure preceding, or immediately following, death.

The tumor was made up of much structureless material, some of which suggested epithelial débris. It evidently was a "pearly tumor," or cholesteatoma.

COMMENT

The following outline will serve to give the sequence of phenomena as they appeared in succeeding attacks.

1. Prodromal[5] (restlessness; request for ice for mouth).
2. Sudden vasodilatation of skin in area supplied by cervical sympathetic nerve. Sudden rise in blood-pressure.
3. Lacrimation. Diaphoresis. Salivation. Dilatation (or contraction) of the pupils. Protrusion of the eyes (not invariable). Increase in rate and pressure of pulse. Marked retardation of respiratory rate. Elicitability of pilomotor reflex. Loss of consciousness (rare).
4. Disappearance of superficial blush and fall of blood-pressure, slowing and weakening of pulse.
5. Hiccoughing (3 to 5 in number).
6. Transient shivering.
7. Cheyne-Stokes respiration (apparently the result but not a part of the attacks).

Blood-pressure. On one occasion the patient's systolic blood-pressure was measured in the brachial artery at 110 mm. of mercury. Just as the determination was finished and before the cuff was removed, the nurse predicted an attack because of the patient's restlessness. The pressure immediately was measured again. It had risen to 190. Deep red flushing appeared. The pressure when retaken was 200 systolic and 100 diastolic. The next determination was 210. The pressure then rapidly fell to 160, 140, and 122 systolic and 75 diastolic. About five minutes after the close of this attack, the pressure was 94 systolic and 68 diastolic. This was a typical attack

[5] The *prodromal symptoms* were not recognized by the patient herself, but her nurse could readily predict an attack thereby. The restlessness was only slight but it was noticeable, as the patient was usually verv quiet between attacks.

and the sphygmomanometric readings would doubtless have been similar had they been taken during the other attacks.

Pilomotor disturbance. On several occasions the nurse recorded in her notes that during the period of Cheyne-Stokes respiration that followed an attack, "goose-flesh" could be seen to appear over the patient's shoulder with each recurring increase in the respiratory rate. During the succeeding periods of apnea, the "goose-flesh" disappeared. This was not always the case. But it was observed that, during the time when the patient was flushed in an attack, a pilomotor reflex could be very readily elicited by stroking the skin of her arms or trunk with a pin. At other times, it was found impossible to elicit the reflex.

Micturition. There was incontinence of urine in one severe attack only. On the other hand, from the onset of each series of attacks until they were over the patient was unable to void and had to be catheterized. This had been found necessary in her previous attacks at home also.

Body and extremities. There was never at any time any body movement to suggest convulsions of the extremities or trunk. The patient lay quietly throughout, and she would usually answer questions in monosyllables.

Temperature control. During the most severe series of attacks the temperature fell well below normal. Neither the very transient shivering that followed each seizure nor the occasional attacks of shivering of longer duration, seemed to cause a noticeable rise in temperature.

Diagnosis. It seems obvious, therefore, that the recurring seizures which the patient suffered, were made up of discharges from the centres which control the vegetative nervous system. Such centres controlling the blood-vessels, the heart, sweating, or temperature, have been placed tentatively by workers on the hypothalamus at about the third ventricle.

The acute softening found in the thalamus of one side, apparently due to the tumor pressure, lay anterior to and above these nuclei. This localized edema was evidently of only a few hours' standing. Four horizontal cuts were made through the basal ganglia of one side. The area of edema extended down as far as the anterior commissure but no farther (Fig. 155, I-IV). This area of edema did not necessarily signify the maximum area of pressure, but for the sake of completeness in the report its description is given. There was also a small cavity farther posterior (as shown in block I, Fig. 155). This also was not over a few hours' standing, as proven by microscopy.

The pressure of the tumor, held loosely as it was in its capsule, was brought to bear upon the thalamus symmetrically on both sides. This pressure came against the dorsal nucleus (anterior) of the thalamus, and the tissue below and anterior to it. The fornices were

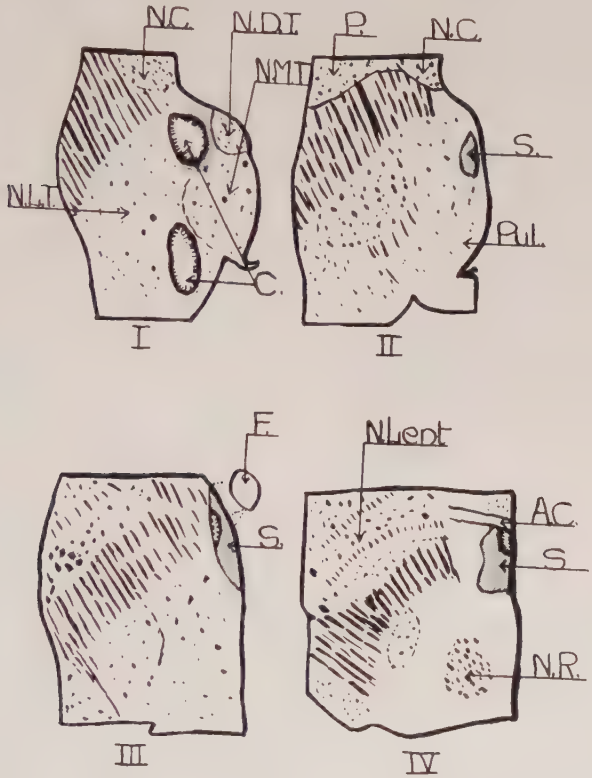

FIG. 155. Horizontal blocks cut through the basal ganglia of the left hemisphere, beginning at the top. *S*, indicates softening; *NC*, nucleus caudatus; *NDT*, nucleus dorsalis thalami; *NMT*, nucleus medialis thalami; *NLT*, nucleus lateralis thalami; *C*, cavity; *P*, putamen; *Pul*, pulvinar; *F*, fornix; *N Lent*, nucleus lenticularis; *AC*, anterior commissure; *NR*, nucleus ruber.

stretched over the tumor. This may account for the complete loss of smell. There must have been pressure upon certain nerve-tracts as well, i.e., the mammillothalamic fasciculus (Vicq d'Azyr), anterior commissure and anterior peduncles of the thalamus.

The tumor contact and pressure was clearly above, and anterior

to, the nuclei of the hypothalamus (Fig. 156), which have been assigned as head ganglia for the vegetative nervous system, being well above the groove which separates the thalamus from the hypothalamus.

It seems to be an inescapable fact that the autonomic convulsions were started by the irritating presence of this movable tumor, intensified by the cerebrospinal fluid pressure on the tumor when it had become wedged into the foramina of Monro, thus shutting off the flow of fluid from the lateral ventricles to the third ventricle. The

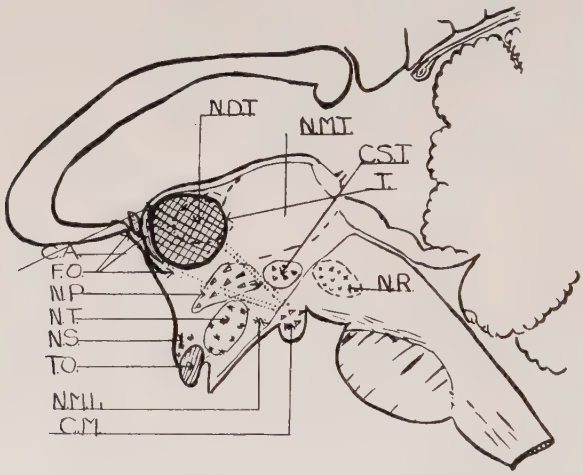

Fig. 156. Site of tumor roughly indicated by cross-hatching on a scheme of paraventricular nuclei. *NDT*, indicates dorsal (or anterior) nucleus of thalamus; *NMT*, nucleus medialis thalami; *T*, situation of tumor; *F*, fornix; *NP*, nucleus paraventricularis (Malone); *NT*, nucleus tuberis; *NS*, nucleus supra-opticus; *TO*, tractus opticus; *NMI*, nucleus mammillo-infundibularis (Malone); *CM*, corpus mammillare; *CST*, corpus subthalamicum (Luys, 2); *CA*, commissure anterior.

history of discontinuous headache, which could be started and stopped by alterations in the position of the head or body, indicates that the tumor, acting as a ball-valve, was at times wedged in between the thalami and at others gave free passage to spinal fluid. This pressure might likewise have caused obstruction in the outflow of the venous blood from the chorioid plexuses, thus increasing to a greater extent the ventricular pressure by augmenting the formation of fluid by the plexuses.

The evidence therefore points to the mechanical irritation of some

centre or conduction path capable of setting into action the ganglia which exert control over the vascular apparatus, the sweat- and tear-glands. One can only theorize in such a case as to what the identity of the structures involved above these centres may be.

It is in a sense a physiological requirement that the thalamus, the structure where painful stimuli rise into consciousness, should have a close connection with the control of those vegetative functions which are almost invariably called into action as a result of severe pain or other strong emotions.

There appears to be no direct downward path from the thalamus to the paraventricular gray nuclei, but Greving (1) points out in his excellent outline that there are fiber connections to these centres from the thalamus by way of the corpus striatum. From the thalamus to the corpus striatum runs the anterior peduncle of the thalamus. From the striate body impulses may pass through the ansa lenticularis via the globus pallidus to the corpus subthalamicum (Luys). There is also probably a direct path, the striohypothalamic. Fibers from the striate body also evidently pass to the nuclei tuberis via the frontotuberal tract and to the nucleus supra-opticus via the fronto-supra-optic tract.

There has been presented what is in some ways the most convincing proof of direct diencephalic control of metabolism within the heart and of epinephrin secretion (Beattie, Brew and Long[6]). Karplus and Kreidl (4–8) have made acute stimulation experiments showing that electrical stimulation of the hypothalamus produces secretion of sweat. It has been suggested that lacrimation and salivation are also under a direct nervous control located somewhere in the hypothalamus.

The phenomena which presented themselves in the convulsive seizures of the patient described, were obviously under direct nervous control, not only from the hypothalamus but also from a neurological mechanism placed somewhat higher.

The production of Jacksonian epilepsy by an irritative focus in the cerebral cortex is analogous to the production of the autonomic epilepsy displayed by this patient. A comparison may therefore be suggested between the region under bilateral pressure from the tumor in this case, and the corticomotor apparatus of the cerebral hemis-

[6] This volume, pp. 249–316.

pheres. It indicates that in the thalamus, and not in the hypothalamus, lies the highest representation of the vegetative nervous system.

CONCLUSION

A series of motor phenomena within the control of the vegetative nervous system have been described, which are analogous to attacks of Jacksonian epilepsy. The irritative source of the attacks was an encapsulated tumor which periodically pressed upon the thalamus of both sides, as described in the preceding account.

Autonomic epilepsy is a new conception in neurology. It is suggested as a result of the study of this case that the vegetative nervous system may have a representation as high as the anterior nucleus of the thalamus. No attempt, however, is made to isolate the centres involved.

DISCUSSION

The following questions submitted to Dr. Penfield before the Commission, together with the answers to them, are here reported verbatim.

Dr. Martin: I should like to ask if the patient had any subjective feelings of anxiety between the attacks?

Dr. Penfield: Apparently not, only the restlessness.

Dr. Hunt: Was there any obscuration of consciousness in the attacks?

Dr. Penfield: In the more severe attacks, apparently, she lost consciousness. In those that were less severe, although she lay perfectly quiet (there was no movement of the body), she would answer in monosyllables any questions asked her, and she would answer them intelligently.

Dr. Kennedy: Was there any alteration of character in this woman?

Dr. Penfield: None whatever so far as I could see. She had a family of two children and all of her neighbors remarked upon her courage and the way she handled her family.

Dr. Miller: Was there any somnolence?

Dr. Penfield: No, unless you call the state in which she lay for days somnolence, when she was having her recurring attacks. She could always answer questions when you asked them, even though she lay with her eyes closed.

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8. ——— and ——— Gehirn und Sympathicus. VII Mitteilung. Über Beziehungen der Hypothalamuszentren zu Blutdruck and innerer Sekretion. *Ibid.*, 1927, ccxv, 667–674.

CHAPTER XXXI

SWIFT'S DISEASE[1]

So-Called Acrodynia, Erythredema, Pink Disease, Erythredema Polyneuritis, Feer's Vegetative Neurosis

ALDRED SCOTT WARTHIN, M.D.

HISTORICAL REVIEW

UNDER various terms there have been reported in the literature about two hundred and fifty cases of a clinical syndrome occurring in young children, which was first described by Dr. H. Swift, of Adelaide, in a paper read before the Section of Diseases of Children, at the Australasian Medical Congress held in Auckland, in 1914. Under the term erythredema, Swift reported a symptom-complex in young children, characterized by extreme fretfulness, neuromuscular disturbance, sleeplessness and a red rash involving the hands and feet and at times other parts of the body. He had noted the occurrence of this syndrome for a number of years; but it had not previously been described. The Transactions of this Congress were not published until 1916 so that Swift's communication was not made available until that time. The London Lancet gave in 1918 the only résumé (45) that was made of Swift's paper; and in May, 1918, Dr. Doak, of Bradford, wrote to the Lancet (12) stating that he had seen at the Bradford Infant's Hospital several patients showing a condition similar to the erythredema described by Swift.

Swift's paper aroused considerable local interest in Australia where apparently the syndrome is more common than elsewhere. At the Brisbane Medical Congress in 1920, A.J. Wood (57) presented notes on eighty-eight of the cases of erythredema collected by himself and F. Hobill Cole between 1917 and 1920. This report was not published until 1921. In it Wood stated that he had seen these cases for the past thirty years, and that before his time it had been recognized by Dr.

[1] From the Pathological Laboratory, University of Michigan.

William Snowball of the Children's Hospital in Melbourne, who spoke of the children with "raw beef hands and feet." He was of the opinion that the disease-complex frequently followed severe attacks of gastro-enteritis and that the prognosis was generally good. Wood states also that the syndrome had long been recognized as an entity in Sydney, where it had usually been spoken of by Dr. C. P. B. Clubbe and others as the "pink disease," so that when recognized by Swift under the term "*erythredema*" it was evidently not an uncommon disease so far as Australia was concerned. These eighty-eight cases collected by Wood and Cole consisted of fifty-two males and thirty-six females, the majority being between eight and eighteen months of age, the youngest four months, while there were only sixteen over eighteen months, the oldest three years and six months old. The chief symptoms presented by these cases were extreme restlessness and fretfulness, irritability, insomnia, profuse sweating, irritating rash over trunk, red, swollen condition of hands and feet which were cold to the touch, photophobia, muscular weakness, stomatitis, intolerable pruritus with secondary lesions due to scratching, loss of weight, with slight fever. The prognosis was regarded as good. Five deaths occurred in a total of ninety-one cases observed by Wood and Cole. Autopsy notes on three are given in this report, but the findings are practically negative as to any especial pathology, the deaths being due to secondary bronchopneumonia. Nothing conclusive as to etiology was offered by the Australian observers.

The next step in the historical development of the knowledge of this disease was an American observation made by William Weston (54) who in 1920 reported eight cases of a similar syndrome occurring in the practice of Dr. W. F. Patrick of Portland, Oregon, which had been referred to Dr. John Lovett Morse of Boston for diagnosis and advice. Dr. Morse feeling that there was a definite suggestion of pellagra in each case referred them in turn to Dr. Weston. The cases ranged from nine months to two years of age, with one of five years, with typical symptoms in accord with the Australian descriptions, and self-limited. The chief interest of Dr. Weston's report is his introduction of the term *acrodynia* as an appellation for the syndrome. He came to do this in the following manner. Consulting Dr. Babcock of Columbia, South Carolina, an authority on pellagra, the latter gave it as his definite opinion that the cases were not pellagra, and suggested that he consult an article by Dr. Henry Strachan of

Kingston, Jamaica, in which he had reported a number of cases (42, 43) which he had described as "malarial peripheral neuritis." Both Sir Patrick Manson and Dr. F. M. Sandwith of London, being consulted in the case, disagreed with the diagnosis made by Dr. Strachan; and Dr. Sandwith in his effort to arrive at a diagnosis, considered pellagra, beri-beri and malarial neuritis, eliminating each, and finally suggesting that the case might be acrodynia. After a search of the literature, this suggestion was accepted by Drs. Babcock and Weston, and so the term *acrodynia* was erronously applied to this syndrome, from its supposed resemblance to an epidemic occurring in Paris, in 1828, which is now known to have been probably arsenical poisoning.

In October of the same year, 1920, J. B. Bilderback (1) reported clinical observations of ten cases of this syndrome which he had seen in his practice during the previous six years. He described the condition, as follows: "It is a disease characterized by profuse sweating without odor, with swollen red feet and hands that are painfully sensitive to touch. The hands and feet are cold and clammy and the skin of the same is in a state of desquamation. The body, legs and arms may or may not have a rash, similar to an erythrema-intertrigo, that at times borders on an eczema and itches. Added to the local symptoms there is a progressive loss of weight and marked weakness and apathy that at times approaches stupor. . . . . The majority [of cases] were children from 1 to 4 years of age who had formerly been healthy and active, who slowly and insidiously became listless and apathetic, losing all desire to play and walk and who wanted to remain in bed. Most of them did not want to sit up even long enough to take food. The three cardinal symptoms were profuse sweating, red swollen hands and feet that were peeling and exquisitely tender, and pronounced asthenia." There were no deaths. Bilderback did not think the condition was infectious, but did consider the possibility of a low-grade toxemia or a deficiency disease. In a later communication (2) Bilderback states that the cases reported by Weston belonged to this group.

In November, 1920, A. H. Byfield (9) reported under the heading, "pellagra-acrodynia," seventeen cases of the syndrome, all under five years of age, five of them being less than one year old. The clinical symptoms were identical with those described by Swift (45), Wood (57), Weston (54) and Bilderback (1, 2). Byfield regarded the disease as a primary one of the nervous system in which there was a

preponderance of sensory manifestations with a mild affection of the motor nerves. He concluded that his cases resembled the acrodynia of Weston or "epidemic erythrema," that it was a disease which seemed to be increasing, and that according to the anamneses, infection rather than dietary error seemed to play the more important rôle as an exciting factor. A postmortem examination in one case (complicated with tuberculosis) showed involvement of an occasional anterior horn-cell of the spinal cord, gliosis about the central canal and edema of the sensory roots. No changes were noted in the dorsal columns. The sciatic nerve showed edema and swelling of the myelin sheath and connective tissue, but no cellular infiltration. Although at first inclined to believe that the disease was one of deficiency,—probably pellagra,—Byfield finally suggested that it has a postinfluenzal radiculitis or sensory polyneuritis. Byfield also mentioned a personal communication from Dr. F. H. Lamb, of Cincinnati, reporting thirteen cases.

In 1921, F. Parkes Weber (52) reported the first European case. It was suggested by Dr. J. H. Sequeira that this case might be an exaggerated example of the erythredema described by Swift (45) and Wood (58), with "raw-beef hands and feet." The following year, Weber (53) again reported the same case, which terminated in death. There was no autopsy. Weber was convinced that this was an instance of the erythredema described by Wood.

During 1921, nine cases were reported by Brown, Courtney and MacLachlan (7). These authors excluded motor neuritis and pellagra, as well as a trophoneurosis, and also any serious dietetic deficiency. They regarded the apparently increased incidence of the disease as due to its relation to influenza. They believed the condition to be a chronic intoxication following or coincident with a chronic respiratory infection. In the same year cases were reported by Miller (30) and by Emerson (13); in 1922 by Porter in California (36), by Vipond (49), Davis (11), Field (17), and Zahorsky (60-62). Vipond reported five cases, in two of which a "diplococcus vaccine" was used, with cure in one and great improvement in the other. Davis reported a fatal case with partial autopsy, the liver only being examined, which showed marked "fatty degeneration." Zahorsky reported five cases, regarded polyneuritis as a prominent symptom, and advised forced feeding of a diet rich in vitamines. In 1923, Bliss (3) reported one case, with improvement in six months under dietetic and hygienic

treatment and exposure to sunlight. In the same year, van der Bogert (4) reported a case, with death from what was termed by the physician "galloping consumption." Diet was incriminated in this case.

In 1922, Thursfield and Paterson (48) report the same case which they had shown before the Royal Society of Medicine in that year, apparently a typical instance of Swift's disease, which they regarded as a peripheral neuritis with skin manifestations. The mental condition resembled that seen in some cases of epidemic encephalitis. While slowly improving, the child died of acute intussusception. No autopsy was made. In 1923, Paterson and Greenfield (35) reported the findings in two necropsy cases, describing changes in the peripheral nerves and central nervous system. They designated the condition as "erythredema polyneuritis." In the same year E. S. Littlejohn (29) of Sydney reported a series of cases; according to his experience the disease was usually seen in the late summer and autumn months, coincidentally with cases of infantile paralysis.

At the Berne meeting of the Swiss Association of Pediatrics, in June, 1922, Feer (15) reported his observations on a "new disease" of which he had seen six cases since 1911. A further study of the condition by him (16), appeared in 1923. The chief symptoms were described by him, as follows: "There occurs in young children an especial neurosis of the vegetative system, which is to be regarded as a disease entity. It shows itself in disturbance of the general state (whining voice, restless sleep, poor appetite), in constant perspiration with its sequelae (miliaria, desquamation of the skin, most marked on hands and feet), cyanosis of the damp and cold peripheral parts (nose, hands and feet), hypotonia of the musculature, lowering of motility, chiefly in sitting, walking and standing, tremor, finally with increased pulse rate and increased blood pressure. The symptoms disappear more slowly than they appear, and after several months there is complete recovery." This is the first continental report of the disease, and at the time of his Bern report Feer had no knowledge of the fact that it had already been described in Australia and in the United States. In a fuller report made in May, 1925, he is fully cognizant of the cases reported by the Australian and American workers. In this later paper he mentions an additional case occurring in a child of four years and five months of age, with autopsy report. The special features of this autopsy were trophic ulcers on the tongue and cheeks,

fingers, and in the bend of both knees. Nothing in the way of gross pathological changes were found in the central nervous system, and the microscopical examination did not show the changes described by the American observers. Feer regarded the disease as a pure neurosis of the vegetative system. According to him the muscle involvement can be explained only in this way. The severe trophic disturbance in the mouth, on the fingers and in the bend of the knees, the loss of sound, unchanged teeth, as well as the changes in the hair and nails, and on the cornea can be interpreted only in favor of the conception of the affection as a vegetative neurosis. Commenting on the nerve pathology reported by Byfield (9), and Paterson and Greenfield (35) in their autopsy cases, Feer is inclined to explain it as secondary to the trophic disturbances, and to discount such pathology as having any primary significance in the disease, since the disturbances are chiefly functional. An ordinary polyneuritis is easily excluded in the diagnosis, since a careful examination shows that there is no true paresis, but only a hypotonia of the muscles, dislike of movement, great fatigue and disturbance of the co-ordinated movements. On the other hand opposing movements are lacking, and the movements of single muscles and the tendon reflexes are preserved. Feer, therefore, holds that the affection should receive the appropriate and unprejudicial appellation of "vegetative neurosis" instead of the inaccurate and confusing terms of acrodynia and erythredema.

In 1924, Braithwaite and Pegge (5) reported a typical case in a female child three years of age, calling attention to the absence of a mouse-like odor, and to the fact also that there was no loss of sensation. In the same year a case with fatal termination in a rachitic child was reported by Szwajkart (46). The year 1925 saw a great increase in the literature of the disease, papers by Fowler ((19), four cases), Bilderback ((2), ten cases), Butler ((8), one case), Oliver ((34), one case), Foerster ((18), one case), Jäger ((25), one case), Jenny ((26), four cases), and Rodda ((39), seventeen cases), following one another in rapid succession. These papers may be consulted for bibliography and full clinical descriptions. They do not advance the knowledge as to the etiology or the pathology of the disease, except in the case of Butler's, in which a biopsy was made of the skin of the hand, and in the case reported by Jenny, in which a full autopsy was made. Jenny regarded the disease as probably infectious in etiology, largely because of its relatively sudden onset.

Fowler (19) thinks that there is little pathological evidence for the conception of the disease as a polyneuritis, except in the one case reported by Paterson and Greenfield (35), and regards it as not impossible that the nerve changes in this case were secondary. He considered that the symptoms of the affection are best explained by Feer's theory that it is a neurosis of the vegetative nervous system. In the discussion on Fowler's cases ((19), pp. 183–184), Dr. John Thomson reported two cases that recovered, except that in one case there have been recurrent attacks of asthma. In 1925 van Westrienen (55) reported three cases and E. S. Frank (20), two cases. All of these cases were typical, and nothing new was added to the previous knowledge in these reports. In August, 1925, G. B. Sweet of Auckland reported five cases (44), apparently typical, in which he saw great improvement from the use of the ultraviolet rays of the mercury quartz lamp.

In January, 1926, Warthin (51) reported a pathological study of two typical cases with necropsy, giving the first full pathological description of the affection. He found no evidence of a polyneuritis as the essential feature of the disease. He did not regard the use of the term erythredema as applicable, since there is no edema of the skin. No relationship to any specific infectious etiology or to tonsillar disease was found. He regarded the pathological picture in his two cases as suggesting either a food deficiency or a toxic state acting on children of the thymic-lymphatic constitution, affecting the reticuloendothelial system of the meninges and skin, the vegetative nervous system, and possibly leading to a light sensitization. He considered the possibility of its being, as was early suggested by Byfield, a condition closely related to pellagra, perhaps an infantile form of that affection. He suggested the name Swift's disease for the syndrome rather than the use of the terms acrodynia and erythredema, which apply so little to the disease.

Alois Bratusch-Martin (6) reported in 1926 a case regarded by the the author as identical with Feer's disease. A case of "acrodynia" was reported in the same year by Pradzynska-Skwarczynska (37), apparently a typical case with recovery after several months. Moro (31) reported a case of Feer's disease with termination in angiospastic trophoneurosis resembling Raynaud's disease. Under the heading, "Acrodynia in Adults," White (56) reported a case in a colored man, aged fifty-two years, which was undoubtedly one of pellagra. Clark

H. Hall (22) reported a case with slow but complete recovery in a male child fourteen months of age. In the same year Domenico Tecilazic (47) reported a case in a child of three and one-half years with fatal termination but no autopsy, which he regarded as arising from a disturbance of the endocrine-sympathetic system leading to a trophoneurosis (neurosis of the endocrine-vegetative system). Kurt Erichson (14) in a report stated that the vegetative neurosis described by Feer had been seen in Germany only five times (Keller (27), two cases; Ihm (24), one case; Jäger (25), one case; and Müller (33), one case). All of these investigators agreed that in "young children there occurs a peculiar neurosis of the vegetative system." Erichson added one case in a child three years and three months old, with symptoms characteristic of Feer's neurosis; the child was treated for bacteremia. He regarded the condition as infective, and stated that all of the German cases began with an infection from which the child failed to recover. In an article in the same year, Vipond (50) stated that he had seen many cases of the syndrome since his first report. He concluded that it was a toxemia of brain and cord due to a small Gram-positive diplococcus, and that it could be cured by the use of an autogenous vaccine. After two doses (6 to 9 days) improvement was noted, hands and feet becoming nearly normal. He regarded all of the symptoms of the syndrome as due to a toxemia.

In 1927 typical cases were reported by Stöhr (41), Robinson (38), Scott (40), Craig (10), Muelchi (32), Goudsmit and Rümke ((21), three cases) and Helmick ((23), a series, number not given). Robinson emphasized the avitaminous nature of the affection, reporting recovery on liberal diet, with cod-liver oil and orange juice. Scott's case improved under treatment. Craig reported a cure on a balanced diet, with cod-liver oil and quartz light; Muelchi reported a cure six months following tonsillectomy. Goudsmit and Rümke believed that the cases collected under the title of acrodynia did not represent a nosological entity, but a clinical syndrome resulting from the action of various toxins (i.e., intestinal toxins, encephalitic virus). The existence in all of these syndromes of digestive troubles and of nervous symptoms in particular, associated with psychical manifestations and trophic and sensory vasomotor disorders, especially in the extremities, created a veritable family of morbid conditions, due probably to an apparent alimentary cause or to the hidden action of a virulent germ. In a report upon "Symptomatology of Acrodynia as a Basis for a New

Line of Investigation as to Its Etiology," A. G. Helmick (23) made general observations on a series of cases seen by him, comparing the symptoms with those of allergy. In one case there was a sloughing of the ends of the toes. The age of his patients varied from four to ten months, temperature was usually normal or subnormal and the active invasion lasted from four to ten months. He considered all symptoms of acrodynia as strongly suggestive of an allergic reaction. Woringer (59) in September, 1927, reported cases, with a full resumé of the disease.

In 1928, Kernohan and Kennedy (28) reported a pathologic study of a case occurring in a boy of twenty-three months, with necropsy. They emphasized especially what they considered to be degenerative changes in the central and peripheral nervous systems, evident in the spinal cord as chromatolysis of some of the anterior horn cells, with changes in the basal nuclei and in some of the nuclei of the medulla oblongata. They found it impossible to draw definite conclusions from the appearance of the tissues in their case, but favored the view that the disease was an infection, the toxic products of which secondarily affected other parts of the body.

Based upón a study of all of the cases reported in the literature up to the present time, insofar as etiology, symptomatology and pathology are concerned, the following condensed abstract gives the leading facts and views concerning this syndrome.

ETIOLOGY

The primary etiological factors of the disease remain unknown. It has been regarded as a postinfluenzal sequela (postinfluenzal polyneuritis, Byfield (9)), as a chronic respiratory infection (tonsils, lungs, bronchi) or an intoxication arising from infections of the upper respiratory tract (Rodda (39)), and as a specific infection of unknown nature (Feer (15, 16), Erichson (14), Jenny (26)), or as due to a specific diplococcus (Vipond (49, 50)). In the cases developing after previous infection there was a definite period of from one to several months before the development of the picture of acrodynia. These previous infections have been almost wholly respiratory-tract infections, although in several cases there was a history of diarrhea occurring just before the onset of the symptoms of hyperirritability. Feer considers the most probable cause to be an unknown infective agent, and that it is less likely to be the sequela of any infectious disease.

Against the view that the disease is postinfluenzal, is Swift's own experience that no influenza preceded it in the Australian cases. The relative frequency of the disease in Australia and in America speaks for some specific agent of infection, as does also the fact that Feer's case and the three reported by Jenny came from the same close neighborhood in Switzerland. The relative sudden onset of the disease was regarded by Jenny as favoring an infectious etiology. Other writers emphasize the *toxic* nature of the affection (Brown, Courtney and MacLachlan (7), Goudsmit and Rümke (21)). Goudsmit and Rümke hold that the affection is not a clinical entity, but a syndrome resulting from the action of various toxins, possibly a rare form of encephalitis with polyneuritic symptoms of an atypical polyneuritis following an enterogenous intoxication. Helmick (23) regards the syndrome as highly suggestive of an allergic reaction, and thinks that all of the symptoms can be explained as allergic in nature. Vipond regards them all as due to a toxemia of brain and cord caused by a small Gram-positive diplococcus. On the other hand, the affection has been considered as an avitaminous or deficiency disease by some observers, notably Byfield (9), Warthin (51), Bliss (3), Bilderback (1, 2), Robinson (38), Craig (10), Wood (57). This theory has been opposed by Feer (15, 16), Jenny (26), Brown, Courtney and MacLachlan (7) and others. The majority of the cases observed were reported as being on a proper diet. Nevertheless, cures are reported on a balanced diet, with the addition of cod-liver oil and ultraviolet light. No relation to rachitis has, however, been shown to exist. The conception of the syndrome as a polyneuritis, as held by Byfield (9), Thursfield and Paterson (48), and Paterson and Greenfield (35), Kernohan and Kennedy (28), is vigorously denied by Feer (15, 16), Fowler (19), Warthin (51), Jenny (26), Erichson (14), Bratusch-Martin (6), Moro (31). The latter group of investigators regard the disease as being in the nature of a vegetative neurosis. Feer considers the changes seen in the nervous system by Byfield and Paterson and Greenfield as having no primary significance and as being purely secondary. Warthin found no nerve-changes. Feer, therefore, rejects wholly the polyneuritic conception of the disease, as unsupported by symptomatology or pathology. Domenico Tecilazic interpreted the syndrome as due to a disturbance of the endocrine-sympathetic system, leading to a neurosis of the endocrine-vegetative system. No relationship to syphilis or to tuberculosis has been found; nor is there any connection

between the disease and arsenical poisoning. There is nothing in the symptomatology or pathology to connect it with the French epidemic of "acrodynia" in 1828. It is notable that the affection is confined to very young children, almost all of the patients being under four years of age. The youngest positive cases occurred at three and one-half to four months; the oldest was reported as being seven years old. Between six months and two years is the period at which the larger majority of cases occur. Male infants preponderate in the reported cases. By far the greater incidence of the affection in America and in Europe has been in the winter and spring; in Australia, on the other hand, in late summer and autumn. Feer has observed in this seasonal relationship a connection between the catarrhal season of the year and the marked catarrh of the nose seen in so many of the cases, as indicating an influence upon the production of secretory-neurotic catarrhs. Moro (31) has also called attention to the springtime as being the season of increased endocrinal activity. The thymic-lymphatic constitution was shown to be present in three necropsies (Jenny (26), Warthin (51)). Complicating disorders were found in only a few cases and appeared to have no etiological relationship.

SYMPTOMATOLOGY

This clinical syndrome consists of three groups of symptoms: nutritional, nervous and cutaneous, occurring in infancy and early childhood, such as loss of weight and appetite, asthenia, fatigue, motor weakness, extreme irritability, sleeplessness, paresthesia, muscle hypotonia, tremor, stomatitis, photophobia, erythema, coldness, swelling and cyanosis of hands and feet, excessive perspiration, miliaria, desquamation, loss of hair and teeth, and high blood-pressure. The affected child may present a dramatic clinical picture of intense misery, marked psychical depression, almost constant whining and movement, pink hands and feet, knee-chest position with head buried in the pillow, chewing of the lips, fingers and toes, and wringing of the hands.

Onset and Symptoms

Onset. The onset of the affection is not sharply defined. A normal, thriving child rather abruptly shows extreme hyperirritability, loses appetite, refuses the breast, sleeps poorly, develops a stomatitis, perspires excessively, and cries and whines constantly, and usually shows marked photophobia. A number of writers have mentioned

severe colds (severe nasal catarrh) or bronchitis as early symptoms marking the invasion of the disease, others have noted an intestinal catarrh as the earliest symptom, but in the great majority of cases the onset begins with a refusal to take the breast well, a loss of weight and constant fretfulness night and day. These symptoms usually precede the occurrence of sweating. The latter is usually well developed before the miliarial rash appears, and the redness and coldness of the hands and feet may not develop until eight to twelve weeks after the beginning of the affection. Stomatitis may be a very early symptom, and is frequently present before the fingers and hands are affected. The disease usually begins without any increase in temperature.

Nutrition. Lessened appetite is usually given by the parents as an early symptom, but in the majority of cases this does not reach such a high degree as to cause much emaciation, except in unusual cases. Usually the general condition remains fair. Vomiting does not ordinarily occur. The loss of appetite may be referred in part to the lessened motility. Most of the cases show normal stools; diarrhea occurs only exceptionally, and is temporary.

Insomnia. In all of the cases there is marked temporary or permanent insomnia, restlessness in sleep, which is superficial and easily interrupted through slight noises. After restless nights some children may sleep much in the daytime, suggesting a resemblance to epidemic encephalitis.

Psychical disturbances. The repressed and whining voice constitutes one of the most striking features of the condition. The face assumes the appearance of an older person, showing misery and apathy, often an expression of severe pain, with wrinkling of the brows. The children weep much in the first stage of the affection and rarely laugh. The cause of the repressed voice is not clear, but according to Feer it stands in direct relationship to a disturbance of the vegetative nervous system which has tracts and centres in the brain. The lessened power of movement in itself is unpleasantly received, interest in play is wholly lost, the children preferring to lie inactive for hours at a time. Nevertheless all cases show a good mental development, and are well oriented as to their surroundings, in which they take an active interest. On account of the age of the children it is difficult or impossible to determine how far painful sensations are responsible for the repressed psychical state. Pain is not elicited by passive move-

ments and pressure on the nerve-trunks. Unpleasant sensations and intolerable itching are very prominent features, particularly in the macerated skin of hands and feet. Apparently there is a close relationship between the repressed psychical state and the excessive sweating, inasmuch as in a case where the latter was controlled by the use of atropine, the voice became normal.

Central nervous system. Except for the disturbances in motility, there are no symptoms referable to the brain or spinal cord. Sensibility shows no disturbances. Hyperesthesia of the legs and hands has been noted in several cases. The sensitiveness to pain is preserved. According to Feer and to Jenny the deep reflexes are well preserved; the patellar in some cases are exaggerated; although the American authors report them as diminished or wholly lost. The electric excitability of nerves and muscles is not disturbed, and not increased. A positive facialis phenomenon may be present. All signs of spasmophilia fail. Meningitic symptoms are wholly lacking; the cerebrospinal fluid shows no changes. The most striking of all is the swelling and bluish-red color of the hands, and to a less extent, of the feet; in many cases there is also a cyanosis of the tip of the nose, and of the vulva. The swelling is not equally marked in all cases; the proximal phalanges are usually more swollen than the distal. As the case progresses, swelling and cyanosis are gradually lost, often producing a patchy effect with wrinkling of the non-swollen areas. The hands and feet are cold and usually moist. Very striking is the excessive perspiration involving all parts of the body. Several writers have mentioned the mouse-like odor of the sweat; others have stated that such an odor was not present. The sweating is so excessive that it is often necessary to change the clothing several times daily. An intense thirst accompanies the sweating; in one case the condition was first thought to be diabetes. Miliarial rashes accompany the sweating, as well as evanescent rashes of all kinds, resembling measles, scarlet fever and German measles. Urticarial exanthemata are frequent. An intense pruritus is present, and as a result of the scratching, secondary infections in the forms of pustules, abscesses, ulcers, phlegmons, and panarities are common; they all run a torpid course. In cases of pronounced dyshidrosis of the hands white vesicles may appear, which through scratching become abscesses and phlegmons, or may finally terminate in gangrene of the phalanges, resembling that of Raynaud's disease (Weber's acrodermatitis mutilans). Loss

of the nails has been frequently observed. Desquamation of the epidermis of the hands and feet occurs regularly; in other cases the picture is that of a maceration. Loss of the hair is a common occurrence. Ulcers occur on the tongue. The eyes, and other sense organs, show no evidences of disturbance.

Vegetative nervous system. The testing of the vegetative nervous system by means of drugs and the Aschner reflex has yielded only negative results.

Disturbance of motility. In all cases marked disturbances of motility are present, showing themselves early in the disease as fatigue and exhaustion in walking, standing and sitting. Most of the affected children kept for weeks or months a recumbent position in the knee-chest position. The power to walk was early affected; in attempting to do so the children often bend the knees and stand on them. A marked anterior flexion of the body usually develops, the child lying for hours at a time with the head between the legs. As the condition improves, the gait becomes insecure, with marked lordosis and extended belly, similar to that seen in progressive muscle-atrophy, congenital luxation, or coxa vara. In contrast to the lowered motility in standing, walking and sitting, the motility of the individual muscles and muscle-groups is well preserved; the movements of the head, eyes, arms and hands, and tongue are undisturbed, although at first hesitating and slow. The legs can be moved, and the body turned to one side or the other. The impression is obtained that the muscle-power is not appreciably weakened, but that the muscle-disturbances depend upon fatigue and lack of inclination rather than upon a true weakness. There appears to be no real atrophy of the muscles of the back and rump, as was at first thought to take place. A lowering of the muscle-tonus is constantly present. In the late cases a slight tremor of the hands, varying from a fine to a coarse form, usually an intention tremor, may be present. In some cases there has been observed a strong general tremor.

Skin and mucous membranes. Changes in the skin are always present and are of a manifold variety, including those of the mucous membrane of cheeks and gums. The teeth begin to loosen, and many of them may be lost. Marked salivation occurs in many cases. All of these changes occur without marked inflammation. In other cases a mild catarrhal stomatitis is common. The loosened teeth appear to be normal. From the nose there is frequently a very abundant sero-

mucous secretion which lasts for months. Occasionally it is accompanied by ulceration of the nasal mucosa. The conjunctivae are frequently inflamed, with resultant marked photophobia. Extensive epithelial defects in the bulbar conjunctiva and cornea may be present, accompanied by a marked flow of tears. An otitis media has been observed in several instances.

Circulatory symptoms. An increase in blood-pressure to 130 mm. Hg. has been observed, although the normal rate in children of this age is from 80 to 90 mm. Hg. There is also a striking tachycardia (130 to 160 in the resting child), in cases without fever and with a normal heart. The study of the cyanotic hands and feet with the capillary microscope showed only a few short capillary segments.

Blood. The blood examination usually shows a normal count, with a moderate oligochromemia. In complications a neutrophile leucocytosis may be present.

Lymph-nodes. These are always enlarged, whether examined early before sweating and skin eruptions have appeared or at a later stage of the disease. Their condition cannot, therefore, be regarded as a secondary symptom, but as one that is dependent upon the original nature of the disease. In Warthin's (51) and Jenny's (26) cases the lymph-nodes were part of a thymic-lymphatic constitution.

Spleen. The spleen becomes enlarged, particularly in cases with secondary infection.

Respiratory tract. Aside from the occurrence of catarrhal symptoms in the beginning of the disease, bronchitis and bronchopneumonia frequently develop as later complications, and may be the cause of death. It has been noted in several patients that in spite of a very abundant discharge they showed little tendency to cough. This has been interpreted as the result of a diminished sensibility of the bronchial mucosa.

Gastro-intestinal tract. Constipation is the rule, although diarrheas may initiate the disease or develop later in its course. No changes in the liver have been observed.

Urinary tract. Pain on urination, many times accompanied by retention, has frequently been observed. A mild cystopyelitis is of such common occurrence that a lowering of the resistance of the urinary passages against infection has been assumed. Acetonuria has often been frequently suspected, but tests for glycosuria have been usually negative. The *body pains* of which many children com-

plain are ascribed in part to the cystopyelitis, and in part to the results of disturbance in intestinal evacuation.

Basal metabolism. Tests made by Brown (7) showed a negative basal and nitrogen balance.

Temperature. The temperature is usually normal. The excessive sweating may be accompanied by a subnormal temperature. Fever occurs in complicating infections (bronchitis, bronchopneumonia, abscesses). In the earliest stages of the disease the temperature is practically always normal.

Course of the Disease

The course of the disease is very chronic. After the symptoms described above have come in a short time to full development, they usually remain from two to four months at their height, then gradually decline and terminate in complete and permanent recovery after from several months to one year. Death may occur from intercurrent sepsis, colitis, bronchitis, or bronchopneumonia. Jenny (26) reported only fourteen deaths out of one hundred and sixty-seven cases. In the most recent paper by Wood (58) he stated that ten deaths occurred in thirty-one patients admitted with this disease to the Melbourne Children's Hospital. In two cases death was quite sudden without explainable pathological reason. The majority of these children were very seriously ill on admission, a fact which may account for the high mortality. In the open air, and out of the city, the prognosis is good as to ultimate recovery, but when it is necessary to send these children into a general or children's hospital the mortality among them is very great. Woringer (59) estimates the general mortality of this disease at about 10 per cent, a figure which is probably a little high. The great majority of cases terminate in complete recovery, no trace of the disease manifesting itself after recovery has once been completed.

Differential Diagnosis

It is not difficult to make the differential diagnosis. The cardinal symptoms are: cyanosis and swelling of the hands and feet, with desquamation; intense pruritus, profuse sweating, with secondary infection of the skin; increasing muscle-weakness, insomnia, tachycardia and increased blood-pressure. Bilderback (1,2) characterizes the chief symptoms as the six P's: Pain, Pinkness, Peeling, Per-

spiration, Paresthesia, Prostration. In the early stages the possibility of tuberculous meningitis and tuberculosis must be considered; although the emaciation, thirst and furunculosis may suggest diabetes; the disturbance of sleep, epidemic encephalitis; the progressive muscle-weakness, a progressive muscular atrophy; the weakened or absent reflexes, a polyneuritis; or the miliaria may lead to the suspicion of scarlet fever. Pellagra, ergotism, myatonia congenita, scorbutus, acrocyanosis and Raynaud's disease will be suggested by individual cases, but are easily differentiated. The exact evaluation of the other symptoms, especially the high blood-pressure and the tachycardia will soon settle the diagnosis.

PATHOLOGY

In the few autopsy cases that have been studied there have been contradictory reports, particularly with regard to the minute changes in the central and peripheral nervous system. Up to Warthin's (51) two cases there have been no thoroughly studied autopsy cases. Skin biopsies have been made in a few cases, and the microscopic changes have been reported. In the ninety-one cases collected by Wood (57, 58) there were only five deaths, four from bronchopneumonia and one from heart-failure. In the ten deaths reported by him since 1920, there were no autopsies, the clinical diagnosis being intercurrent sepsis, colitis and bronchopneumonia with two unexplained sudden deaths. As to the occurrence of any specific pathologic changes in their fatal cases, the Australian observers report only negative necropsy findings. Byfield (9) saw four deaths in seventeen cases, one from deep phlegmon, one from miliary tuberculosis, the other two from inanition and pneumonia. In one of his cases Byfield reported the finding of a gliosis about the central canal of the spinal cord, with poor staining of the anterior horn cells proximal to the anterior commissure; the dorsal columns were normal. In the sciatic nerve there were edema and swelling of the myelin sheaths in the fibers of the root and in that portion of the nerve lying between the ganglion and the spinal cord. These changes Byfield interpreted as being in the nature of a postinfluenzal radiculitis or a sensory polyneuritis. He suggested also the possibility of an infective trophoneurosis.

Paterson and Greenfield (35) reported the findings in two autopsy cases. They found destruction of the medullary sheath in individual

fibers of the peripheral nerves, particularly in the small bundles of nerve-fibers in the calf-muscles. In the popliteal space only a small number of the fibers of the main nerve-trunks showed myelin degeneration. In the central nervous system there was a diffuse increase of small cells in the gray matter, especially in the lumbosacral enlargement. The nerve-roots also showed some cellular increase, but little meningeal or perivascular exudate was found. In one of the cases there were marked changes in the motor nerve-cells of the ventral horns, particularly in those supplying the distal portion of the limbs. These changes consisted of moderate chromatolysis, eccentricity of the nuclei, and vacuolation of the cytoplasm. They were interpreted as the reaction of the cell-body to the degeneration of the peripheral part of the axone, and they are usually present to a greater or less degree in polyneuritis. The character of the apparent infiltration of the nerve-roots and the gray matter of the spinal cord was not established. The cells appeared to be derived from the sheath of Schwann in the case of the nerve-roots; in the cord they suggested a glial origin rather than a lymphocytic reaction. In the degenerated calf-muscle the great increase of cells was probably the result of the multiplication of the sarcolemmar nuclei (atrophy). One of their patients died of intussusception, the other of a generalized tuberculosis. They regarded the condition as an erythredema polyneuritis.

In the case examined by Davis (11), an incomplete autopsy was permitted, the liver only being examined. The microscopic examination of a small piece of this organ was described as showing "fatty degeneration and infiltration of the liver."

Oliver (34) reported the findings in an autopsy case, in which there was necrosis of the mandible. The hands and fingers were spindle-shaped, with much scarring. The skin was thick and leathery. Sclerosis of the cranial bones was found, abscesses of the sacral region and left lung, cloudy swelling of the heart, liver and kidneys, and an accessory adrenal gland.

Feer (15, 16) reported an autopsy case in a child four years and five months of age, with trophic ulcers on the tongue and cheeks, the fingers and in both knee-bends. No gross pathology was found in the central nervous system and the microscopical examination did not show the nerve-pathology described by Paterson and Greenfield and Byfield. There was no evidence of polyneuritis.

Jenny (26) reported the autopsy findings in a girl aged twenty-seven

months, as double pneumonia, chronic splenic enlargement, cloudy swelling of the kidneys, ascaridiasis, enteritis, atrophy of the thymus, hyperplasia of the lymphoid apparatus, hypoplasia of the adrenal medulla, diffuse colloid struma partly fibroid, and cardiac hypertrophy. No changes were found in the central or peripheral nervous system.

Parkes Weber (52, 53) made a skin biopsy from the border of an ulcer in the foot of his patient, for the purpose of determining whether the lesion was tuberculous. The corium was infiltrated with lymphocytes, plasma cells and fibroblasts. No giant cells were present, and no tubercle bacilli were found.

Butler (8) described the microscopic findings in a biopsy taken from the hands of his patient, a boy of five years. The biopsy and tissue examination were made by Michelson, who gave the following report: The striking feature was the marked hyperkeratosis; there was no parakeratosis. The stratum lucidum was visible; there was some ballooning of the cells of the granular layer; the basal layer was intact. There was no acanthosis. In the corium there was a slight infiltration of lymphocytes, arranged in small strands or clumps. Some fibroblasts were also present in these areas. There was considerable edema of the corium (not shown in his photomicrograph) but nothing in the section that was pathognomonic. The marked hyperkeratosis and the edema alone differentiated the section from the same area in a normal child.

The most complete pathological study that has apparently been made of the disease is contained in the two thorough autopsy reports made by Warthin (51) on two boys, one aged twenty-three months, the other ten months. Autopsy and microscopical examinations are given in full in the original article, but the final pathological diagnoses are repeated below.

Autopsy Reports

Case 1. The findings showed acute fibrinopurulent lobular pneumonia of both lungs, most marked in the right lower lobe; older localized meconium aspiration pneumonia; hypoplastic lymphatic constitution; fibroid atrophy of the thymus; hypoplasia and lipoidosis of the adrenals; hyperplasia of the bronchial, mediastinal, mesenteric, intestinal and retroperitoneal lymph-nodes, with marked exhaustion of the germ centres; acute catarrhal gastro-enteritis; marked congestion and edema of the meninges, brain and spinal cord; atrophy of the fat tissues; hyperkeratosis and parakeratosis; erythema of the skin with reticulo-endothelial proliferation in the papillary layer and corium (so-called acrodynia or erythredema, Swift-Feer disease).

Case 2. The examination showed terminal bronchopneumonia; pulmonary congestion, stasis, edema and localized atelectasis; hyperkeratosis and erythema of the skin (clinical diagnosis of acrodynia); reticulo-endothelial hyperplasia of the corium; atrophy of the panniculi; extreme edema of the meninges, cord and brain; dilatation of the central canal of the cord; fibroid atrophy of the thymus; hyperplasia of all lymphoid tissues, with exhaustion of the germ centres; hypoplasia of the heart and aorta; lymphatic constitution; subacute catarrhal enterocolitis; passive congestion, atrophy and slight parenchymatous degeneration of all organs.

It is noteworthy that the essential pathological features in these two cases were identical. No changes were found in the central or in the peripheral nervous system beyond extreme edema and a slight meningeal reaction, although careful study was made of the brain, spinal cord and peripheral nerves. Acute infection of the respiratory tract was present in both cases, in one the process was older. Both showed gastro-enteritis. No other infective processes were present. Both cases showed marked features of the hypoplastic lymphatic constitution. In both were noted extreme congestion and edema of the central nervous system, with reticulo-endothelial proliferation in the meninges. In neither was there evidence of a polyneuritis. In each the same pathological changes in the skin were present in the form of hyperkeratosis, slight pigmentation, chronic erythema without edema, hypertrophy of the sweat-glands, and perivascular reticulo-endothelium. Both cases showed inanition, and serous atrophy of the adipose tissues.

The essential pathological changes in these two cases would appear to be: extreme edema and slight meningeal irritation of the central nervous system, chronic erythema of the skin without edema, with hyperkeratosis, hypertrophy of the epidermis and sweat-glands, with slight pigmentation of the rete, occurring in children of the hypoplastic lymphatic constitution, with associated or terminal respiratory infections, gastro-intestinal catarrh and inanition. These two cases do not support the theory of a polyneuritis as the essential feature of the disease; neither do they justify the use of the term erythredema as a fitting designation, since they showed no edema of the corium; they do not present any evidence of a specific infectious etiology; they likewise show no relationship between tonsillar disease and the syndrome. Warthin (51) was impressed with the striking resemblance of the skin changes to those seen in the early erythema stages of pellagra, roentgen-ray and ultraviolet-ray erythemas, and in certain forms of light sensitization, xeroderma and fogopyrism. He thought the entire

anatomic picture in these two cases suggested either a food deficiency or a toxic state acting on persons of the hypoplastic constitution, affecting the reticulo-endothelial system of the meninges and skin, the vegetative nervous system, and possibly leading to a light sensitization. He regarded the condition as probably closely related to pellagra, as perhaps an infantile variety of that affection.

Woringer (59) mentions autopsy cases (number not given) by Masson in which particular attention was paid to the glands of internal secretion. He found a hypertrophy of the chromaffinic tissue with signs of increased hypophysis function. Other pathological changes in various organs and tissues showed nothing characteristic. They were such as might be found in every chronic infection with cachexia.

The most recent pathological study is that made by Kernohan and Kennedy (28), in the case of a boy of twenty-three months of age, in which the autopsy was performed two hours and fifteen minutes after death, with the body showing a postmortem perforation of the cardia of the stomach. There was a slight bilateral bronchopneumonia. There was a slight prominence of the solitary lymph follicles and Peyer's patches of the intestine. No mention was made of the regional lymph-nodes, nor of the thymus gland. The brain and cord were described as entirely normal in the gross examination. No mention was made of a microscopic examination of the skin. The chief portion of the pathological study was devoted to the supposed pathological changes occurring in the peripheral nerves, spinal cord and brain. These changes were essentially degenerative in character in the form of fragmentation of the myelin sheaths, degeneration of the Nissl granules and chromatolysis of the ganglion-cells. There was no evidence of any acute or chronic inflammation. Chromatolysis of the ganglion-cells was particularly noted in the dorsal root ganglia and in the Gasserian ganglia. It is highly probable that these acute degenerative changes seen in the nerve-fibers and ganglion-cells were purely *postmortem* changes and of no pathologic significance. Their scattered and patchy character, the total absence of any reaction, together with the associated advanced postmortem changes in the stomach all indicated their postmortem character. Moreover, it is just this type of postmortem degenerative change in the nervous tissue that is so frequently mistakenly interpreted as having pathologic significance. The same criticism applies to the changes in the nervous system described by Byfield (9), and Paterson and Greenfield (35).

NATURE OF THE DISEASE

With regard to the essential nature of the disease, the question cannot be considered as settled at the present time. It is certain that the affection consists of a well-defined symptom-complex which may be conceived of as an independent illness, and not merely as the expression of a general neuropathy. The definite chronic course of the disease, its limited duration and its termination in complete recovery after several months, all speak in favor of its being an independent affection. It is probable that some of the reported cases represent mistaken diagnoses for certain forms of encephalitis. It seems certain that no true polyneuritis is present. The nerve-changes described by Byfield (9), Paterson and Greenfield (35) and Kernohan and Kennedy (28) were not seen by Feer (15, 16), Jenny (26) or Warthin (51), and are probably to be interpreted as postmortem in character. The preservation of motility of individual muscles, and of the reflexes, with the electric excitability, as well as the absence of sensory disturbances, all speak against the diagnosis of polyneuritis. There is a certain resemblance in the changes seen in the hands and feet to the vasoconstrictor neurosis of the extremities, to acro-asphyxia chronica, acrocyanosis and Raynaud's disease, but these conditions do not exhibit the general symptoms of the disease. Feer's view that the affection is a neurosis of the vegetative nervous system, explains most of the symptoms,—the excessive sweating with miliaria and maceration of the epidermis, the tachycardia, the high blood-pressure, the disturbances of the motor apparatus, the muscle-hypotonus, restriction of motility and tremor. The cyanosis, coldness and maceration of the hands and feet are best explained as a constriction of the small blood-vessels and capillaries, which would also explain the high blood-pressure (hypertonia of the sympathetic nerves). Feer (15, 16), therefore, has assumed a neurosis of the entire vegetative system as affording the best explanation of the symptoms of the disease. Efforts through pharmacologic studies to gain a better insight into its nature were, however, unsuccessful. In conclusion, present knowledge leads to the interpretation of the disease as *a neurosis of the vegetative nervous system associated with or dependent upon an infection, toxemia, or a food deficiency, with a possible light sensitization.*

THERAPY

A regimen of fresh air day and night, fresh milk, fresh fruit, cod-liver oil, a balanced vitamine-rich diet, ultraviolet-ray treatment, little or no clothing and no attempt made to amuse the children, will be followed by recovery in three months or longer. Local treatment of the skin with alcohol rubs and dusting with a drying powder, painting with iodine tincture reduced to half strength with alcohol, are advised. The stomatitis may be relieved by swabbing or washing with hydrogen peroxide or listerine solutions. The sweating may be controlled by the use of formalin, or tannic acid washes, or by the use of atropine. Feer (15, 16) thought that the use of calcium lactate (10 gm. daily) or calcium chlorate (5 gm. daily) gave good results in some of his cases.

NOSOLOGY

The term acrodynia is wholly erroneous and should no longer be applied to this condition. Likewise, Swift's term, erythredema, is faulty in that no edema is present. The use of polyneuritis in this connection is not justified by either the clinical or pathological findings. Feer's "vegetative neurosis" does not cover the whole ground. It is, therefore, suggested what the affection be styled simply "Swift's Disease," until more light is thrown upon its etiology.

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CHAPTER XXXII

TUMORS OF THE VEGETATIVE NERVOUS SYSTEM[1]

MONT R. REID, M.D.

INTRODUCTION

IN CONSIDERING the neoplasms of the vegetative nervous system, the embryological development of this system must be borne in mind. Through the cells composing the primitive neural tube, the so-called neurocyte, the autonomic system is related to the somatic nervous system. Certain undifferentiated cells called neuroblasts migrate ventrally from the neural tube, giving origin to the sympathetic ganglia and to the chromaffin tissue. This, in the human being, is located for the most part in the medulla of the suprarenal gland, but is also found in the so-called carotid, aortic, cardiac, tympanic and coccygeal glands, and in the *gelben Zellen* of the crypts of Lieberkühn in the gastro-intestinal tract. Consequently any consideration of the tumors of the vegetative nervous system involves a study of the tumors of the chromaffin tissues.

Tumors of the vegetative nervous system may be conveniently classified as: neurocytoma, neuroblastoma, ganglioneuroma, paraganglioma, neuroma.

NEUROCYTOMA

From the neural epithelium arises the neurocytoma, a single case of which, originating in the neighborhood of the Gasserian ganglion, was reported by Marchand (52, 53).

NEUROBLASTOMA

Neuroblastoma is the name most commonly applied to the malignant tumor that apparently arises from the neuroblasts or undifferentiated cells from which the autonomic and chromaffin systems develop. Other terms are: ganglioma embryonale sympathicum (Pick (70), Wolbach and Morse (85)); sympathicoblastoma (Pick and Bielschowsky (71), Capaldi (15), Bailey and Cushing (5)); sympathigomon (Herxheimer (29)).

[1] From the Department of Surgery, University of Cincinnati College of Medicine.

The larger neuroblastomata and metastases are nodular masses of rather firm consistency. Gross section shows them to be surrounded by a thin layer of fibrous tissue and to contain numerous thin-walled vessels. The cut surface is glistening white in color and from it a pearly juice can be expressed. Intermingled with the glairy white tumor-tissue are a variety of colors— orange, red and black, such as are often seen in xanthoma which are due to hemorrhage, the blood-pigment being in various stages of degeneration. In the larger nodules central necrosis occurs, giving rise to cavities filled with clear or brownish fluid. Microscopically the tumors are alveolar in topography, the septa consisting of delicate connective tissue and thin-walled blood-vessels. The cytology of the tumor-cells is somewhat variable, all stages of cells from neuroblasts proper to more mature and even differentiated ganglion-cells being found in certain tumors. The predominant cells in the pure neuroblastoma are small, being little larger than the lymphocytes, and contain a relatively large, deeply chromatic nucleus with only a minute amount of protoplasm. In the most typical growths, certain of these cells are arranged in rings surrounding a central mass of fibers, the so-called "rosette" formation, a structure particularly characteristic of this type of neoplasm.

The cytology seems to vary with the rapidity of the progress of growth and with the age of the host. Thus the more rapidly growing tumors occurring in the new-born or very young infants, are made up almost entirely of the small neuroblast type of cell, while in older patients or in less malignant growths, mature ganglion-cells with fibril formation may be seen (Landau (40)). Indeed, neuroblastomata and ganglioneuromata may occur in juxtaposition or may be intermingled in the same tumor. The fibrils have been thought to be nerve-fibers; but their failure to stain with silver-tannate by appropriate methods, argues against this point of view.

Metastases from the primary growth extend first to the neighboring lymph-nodes, and thence to the liver, bony thorax and bones of the calvarium and orbit, the course being apparently by the lymphatic channels. But widespread liver and lung metastases, such as those following dissemination by way of the blood-stream, are also known to occur (Anderson and Shennan(3)).

There are reported in the literature sixty-eight tumors which, the author believes, may be accurately classified as neuroblastomata. Forty-three of them were located in the medulla of the suprarenal

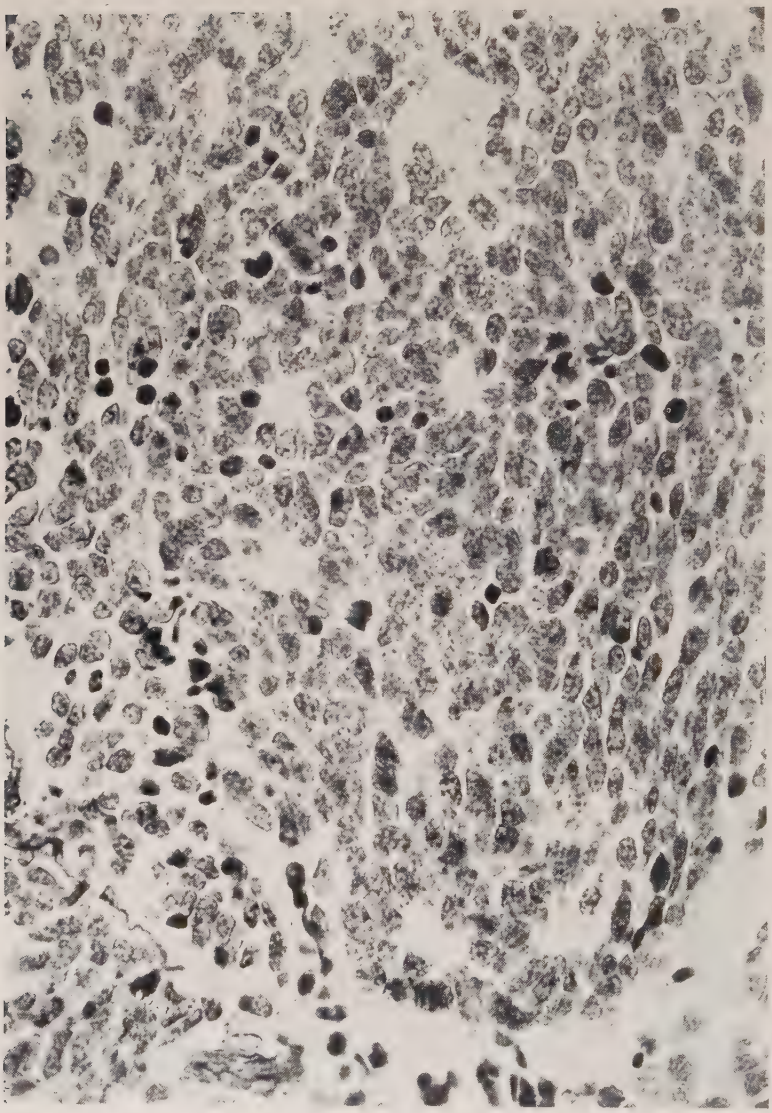

Fig. 157. Histological appearance of a neuroblastoma.

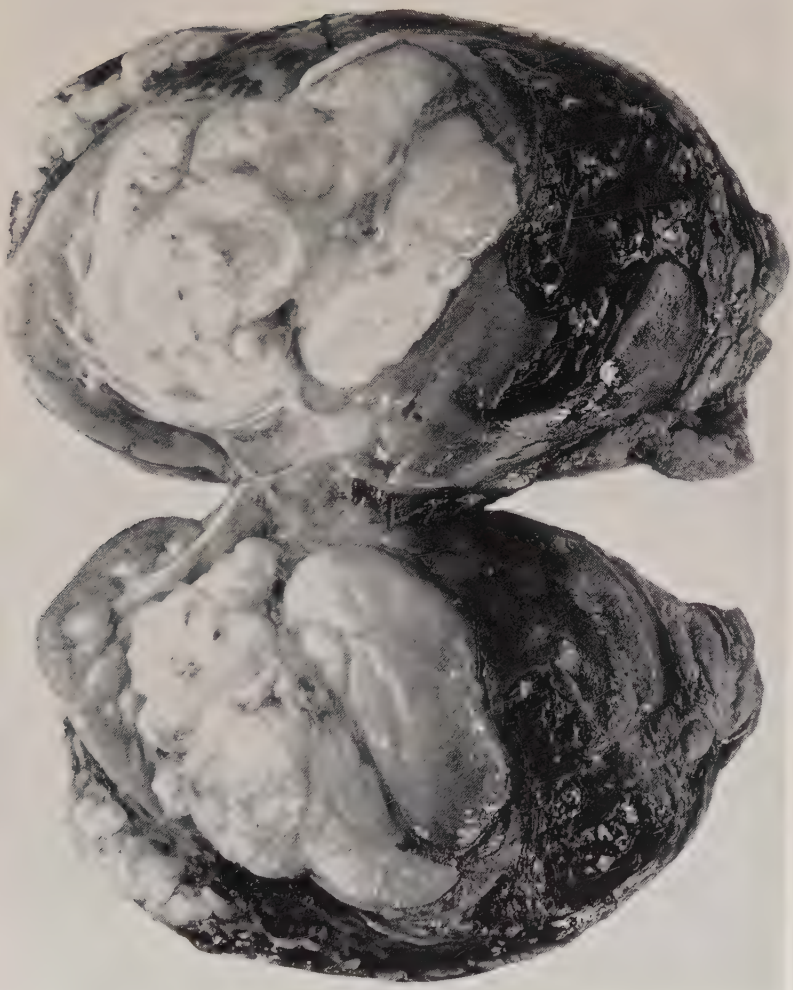

FIG. 158. Renal blastoma. Grossly this tumor resembled a neuroblastoma. Microscopically many of the slides show areas that are almost identical with the "rosette" formation seen in neuroblastoma. Renal tubules, however, were demonstrated.

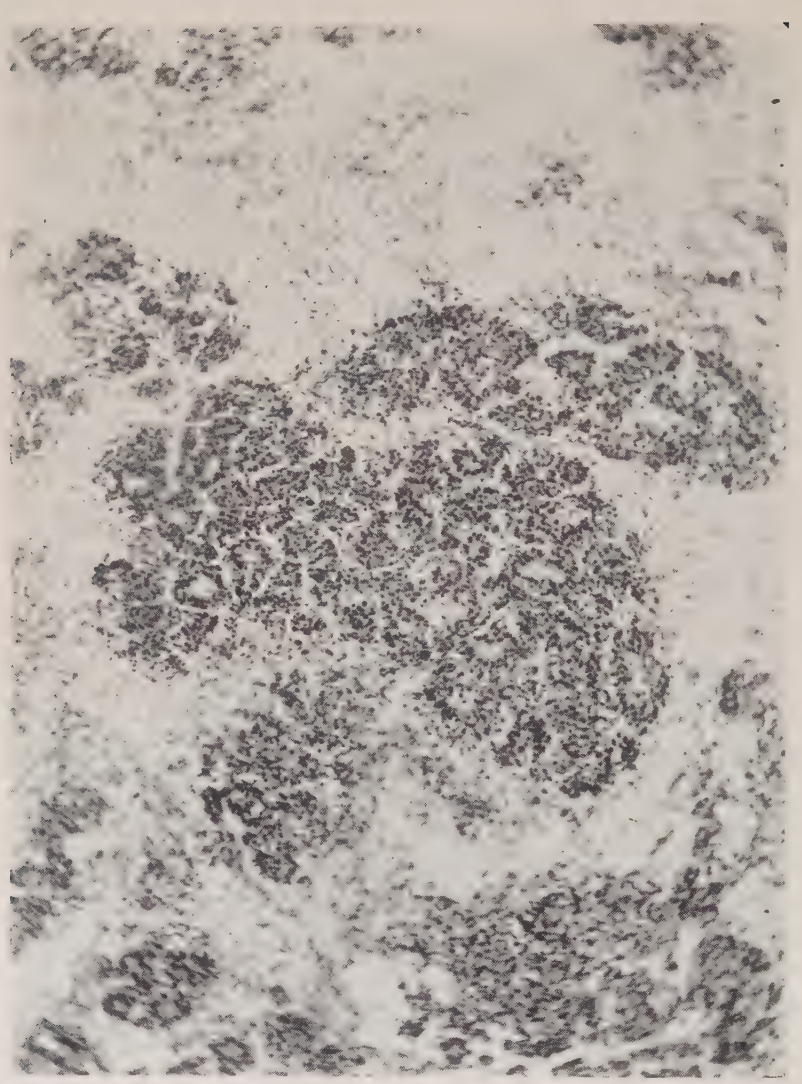

Fig. 159. Low-power picture of a portion of renal blastoma simulating a neuroblastoma. (Stain: hematoxylin and eosin.)

FIG. 160. Tubule formation in the renal blastoma. (Stain: hematoxylin and eosin.)

gland; five, in the region of the central nervous system; one, in the retina; one, in the nasal cavity; two, in the cervical sympathetic chain; three, in the thoracic sympathetic chain; seven, in the abdominal sympathetic chain; one, in the uterus; two in the region of the coccygeal gland; two, in the small intestine; and one, in the stomach.

This neoplasm occurs predominantly in infancy or early childhood, several have been congenital. Eight per cent of the patients, were less than two and one-half years old, but seven cases (Ritter (76) and Meltzer (64)) have recently been reported in patients over forty years of age.

The site of predilection is in the suprarenal gland, as is shown by the fact that in forty of the cases the primary growth was found within this organ. In one case, both suprarenals were involved. From very small, primary tumors (8 mm. in diameter in one case) metastases in the liver, lymph-glands, and other organs, may occur and reach considerable size. The smaller tumors may be confined to the medulla and thus appear simply as an enlargement of the suprarenal gland (Pepper (69)). In a small percentage of cases, the existence of a tumor in the suprarenal medulla has been heralded by the symptoms of Addison's disease, notably asthenia and cutaneous pigmentation. However, in the larger proportion of cases the growth has not become evident until widespread metastases have produced pressure effects either in the abdomen or in the intracranial contents.

Two clinical types have been differentiated: the first, which because of intracranial or retro-orbital metastases, appears with exophthalmos, epileptiform seizures or paralyses; and a second group, in which progressive enlargement of the abdomen is the first symptom. The primary diagnosis of neuroblastoma in the absence of a biopsy has rarely been made, but this growth should be suspected, particularly in young children, when a mass is found in the region of the suprarenal gland with characteristic metastases, or when the liver is markedly enlarged without pronounced ascites. The presence of Addison's syndrome would be of definite aid in the early diagnosis, but this unfortunately occurs in only a small number of cases. Moreover, about 38.5 per cent of these tumors have their primary origin in other parts of the body, notably in the sympathetic nervous chain and the gastro-intestinal tract.

As has been noted by Hutchison (33), Boyd (11), Wright (86), and others, the first evidence of trouble may often be due to metastases in

the head. The appearance, in a child, of swellings about the bones of the skull, the protrusion of one or both eyes, the discoloration of the lids and a profound secondary anemia, are conditions that should arouse suspicions of the presence of a neuroblastoma. Increased intracranial pressure, drowsiness, optic neuritis and blindness may follow. In some cases the exophthalmos has been so marked as to cause the ulceration of the cornea and the escape of the lens from the eye. In about half the cases in which the symptoms are due to the cranial metastases, an abdominal tumor may be palpable. Boyd has called attention to the peculiar type of periosteal reaction and calcification that occurs in the metastases. He speaks of the skull in some cases as having a "porcupine" appearance. Due to this unusual proliferation of bone in the metastases Holmes and Dresser (31) have recently presented the X-ray studies in three cases, from which they conclude that the roentgenograms may be pathognomonic of the condition. This observation is of sufficient diagnostic value to warrant the inclusion here of a copy of the report of one of their cases.

Case History

History. A boy, aged four years, who entered the hospital September 30, 1927, had complained of swollen and tender joints nine months previously and had shown a disinclination to walk. A month before admission, conjunctival hemorrhage and protrusion of the left eye developed.

Examination. The child was pale, emaciated, poorly developed, very weak and apparently suffering great pain on attempted motion. There was marked prominence of the veins of the forehead, very pronounced exophthalmos of the left eye with edema of the lids, and some conjunctival hemorrhage. Numerous hard, small glands were felt in the neck, axillae, epitrochlear regions and groins. The liver and spleen were palpable, but otherwise abdominal masses could not be determined. The pulse-rate and temperature were elevated. There was evidence of a severe secondary anemia. Blood-examination revealed: red blood-cells, 1,620,000; white blood-cells, 9,000 to 13,000; hemoglobin, 32 per cent. The Wasserman reaction was negative. The tuberculin test was also negative. The urine showed a trace of albumen upon one examination, sugar in three specimens, acetone and diacetic acid once.

X-ray examination showed a widespread pathological progress involving both the flat and the long bones. The long-bone involvement extended as far as the midshaft of the bones of the leg and fore-arm. The process was both destructive and proliferative in character. The long bones showed definite periosteal thickening, in addition to small areas of destruction. The skull and pelvis presented a diffuse mottling, which on close inspection appeared to be due to myriads of small foci of diminished density. A metastatic neuroblastoma was at once strongly suspected from the X-ray observations alone. In view of the extensive bone involvement and the poor condition of the patient, irradiation was contra-indicated.

Course. The child grew steadily worse. The exophthalmos increased and numerous small nodules appeared scattered over the skull. These nodules increased rapidly in size, and signs of intracranial pressure developed. On October 30, moist râles developed in both lungs; and on November 1, the child died.

Autopsy. Gross examination. At autopsy no fluid was discovered in the peritoneal cavity. The retroperitoneal glands were enlarged. Many were firm and hard, others were soft and necrotic. The left suprarenal gland was normal. The right was composed of an encapsulated, hard, nodular tumor measuring 6 x 9 x 4 cm., lying on the upper pole of the kidney and extending down on the kidney pelvis. There was slight adherence to the liver. The cut section of the tumor showed a lobulated surface composed of circular areas, the largest a centimeter in diameter. Some of these areas were fibrous in character, some contained calcium and some were necrotic. The underlying stroma was a firm, fibrous-like tissue. The right kidney was normal. The liver was enlarged but did not contain tumor-tissue. There was no tumor-tissue in the spleen. The tibial and femoral condyles were invaded by nodules of tumor-tissue which caused ulceration and necrosis of the bones, but without evidence of fracture. There was no fluid in the pleural cavities. The lungs were clear. The aorta was surrounded entirely by enlarged glands, but was not itself involved.

There was marked protrusion of the left eye, due to a tumor growth in the orbit. Numerous tumors, varying in diameter from a few millimeters to 3 or 4 cm., were seen growing from the periosteum of both external and internal surfaces of the skull, eroding the bone slightly on the outside and very extensively on the inside, but nowhere perforating the skull. A number of these tumors had broken down into a thick purulent material. The brain was normal. The arches of the vertebrae were softer than normal. Tumor-like masses were found lying posterior to the spinal cord throughout its length; they were most numerous in the cervical and upper dorsal regions. There were no changes in the cord itself.

Microscopic examination. The suprarenal tumor consisted of small, undifferentiated tumor-cells with a densely scirrhous stroma. There was marked necrosis, and in some areas calcification. The tumor was evidently of long standing. Metastases in the regional lymph-nodes showed more definite differentiation. The tumor-cells were slightly larger than lymphocytes, and in many places were grouped in alveolar arrangement; in a few places there was definite "rosette" formation. In the centre of the "rosettes" a fine fibrillar structure could be discerned, which failed to stain with phosphotungstic acid, hematoxylin, or aniline-blue. Bielschowsky stains were also unsatisfactory. The fixation was poor, but the structure was very suggestive of a neuroblastoma. The same general arrangement was noted in the metastases to the skull, but the fixation was too poor for careful histological differentiation.

The periosteal reaction and the regeneration of new bone are the uncommon features of the disseminated neuroblastoma, and may explain the fact that spontaneous fractures have not been recorded. Except for this the metastases of carcinoma or myeloma might simulate those of neuroblastoma.

The prognosis in cases of neuroblastoma is bad, only one patient, reported by Lehman in 1917 (41), having been successfully operated upon. In that instance, the tumor was confined to the suprarenal gland, which had become enlarged and pedunculated and could therefore be completely excised. Thus far, irradiation has had no appreciable effect in the treatment of neuroblastomata.

GANGLIONEUROMA

These tumors vary considerably in size, those reported ranging from the size of a hen's egg to that of a child's head or larger. In Sauerbruch's (78) case (reported also by Brunner (13)) the tumor measured 17 x 12 x 8 cm. Due to their large fibrous content they are firm in consistency, presenting in the gross many of the characteristics of a fibroma. In some instances, the outer layers of the tumor form a very firm, almost cartilaginous shell enclosing a mass of softer tissue. The cut surface is gray and glistening and appears to be relatively avascular, with fibrous-tissue septa dividing the tumor into smaller lobules. Microscopically these neoplasms show a rather coarse, reticular arrangement of fibrous tissue in the interstices of which are contained strands of non-medullated and medullated nerve-fibers. In the majority of cases the former type predominates. Intermingled with these fibers are found multipolar ganglion-cells varying in number in different tumors and many of them showing signs of degenerative changes, such as vacuolization (Stout (82)).

The ganglioneuromata are usually benign, as is shown by the fact that they are of slow growth and may reach a considerable size before giving rise to symptoms. In Sato's case (77), the tumor was known to have been present for sixteen years before its operative removal. Several other authors (Borst (10), Beneke (6), Ohse (67), Braun (12), Krecke (38), and Brunner (13)) have reported cases in which the tumor was as large as a child's head or larger. In at least one instance (Busse-Kredel discussed by Busse (4)), re-investigation of a ganglioneuroma, incompletely removed at operation five years previously, failed to reveal any recurrence. In certain of the reported cases, ganglioneuromata seem to have possessed malignant characteristics. Thus, Beneke (6) observed cell-types and topography suggestive of neuroblastomata, while Berner (8) and Miller (65) found metastases from such a tumor in the neighboring lymph-nodes. Jacobsthal (34) noted liver metastases, and Seefelder (80) described metastases from a pelvic ganglioneuroma to the lymph-nodes, bones and soft parts.

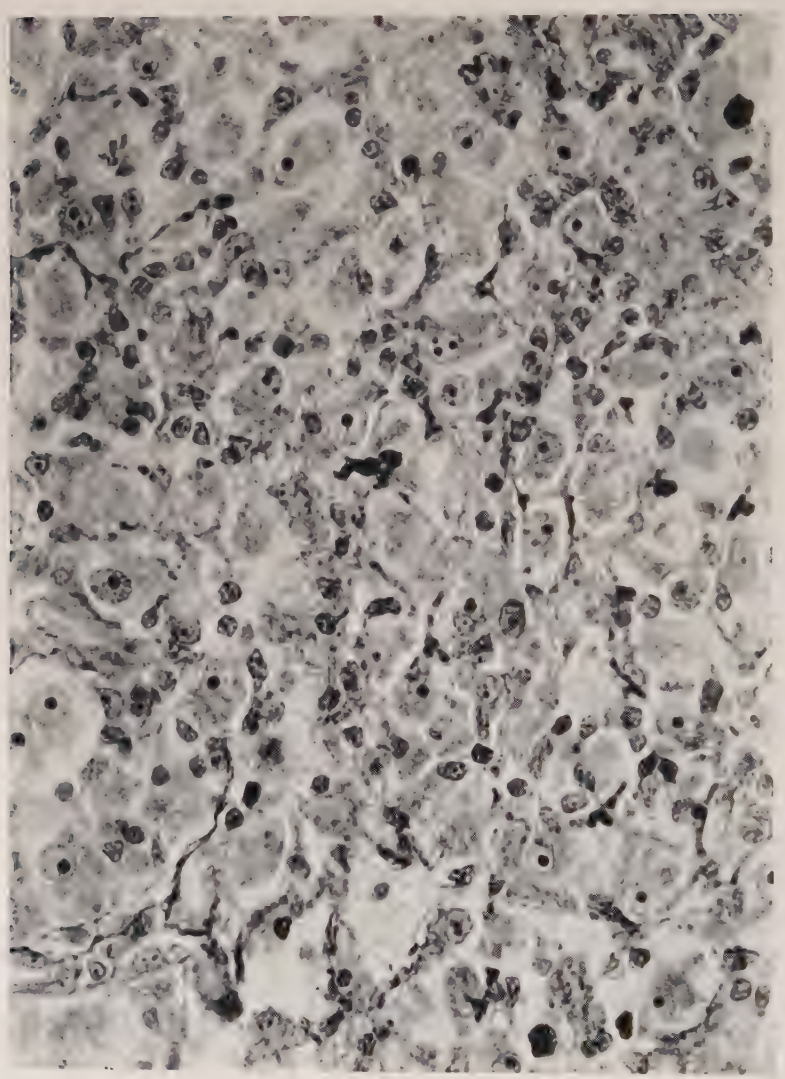

FIG. 161. Histological appearance of a ganglioneuroma. Note the large ganglion-cells.

These cases have been taken to indicate the malignant degeneration of ganglioneuromata. However, since combinations of neuroblastoma and ganglioneuroma are known to exist, it would seem more rational to consider these cases as neuroblastomata in parts of which more mature elements, i.e., differentiated ganglion-cells, are to be found (Cushing and Wolbach (16), Dunn (19)). Indeed, it seems altogether likely that there are all gradations between pure neuroblastomata and pure ganglioneuromata, and that the degree of benignancy corresponds quite accurately with the degree of differentiation to be found in the individual tumors. The rather rare occurrence of ganglioneuromata in connection with peripheral nerves may be due to anomalous development, but is also to be explained by the presence of ganglion-cells, which have been found in the brachial and lumbosacral plexuses in various animals. Diffuse subcutaneous distribution, such as occurred in the case of Kredel-Beneke (39), may originate from the perivascular plexuses in which ganglion-cells have been demonstrated (Glaser (24)).

In contrast with the neuroblastomata, the ganglioneuromata occur more commonly in adults, the average age in fifty-two cases being nineteen years. The youngest reported patient was four years of age and the oldest seventy-five. Sixty-two per cent of the cases occurred in females, while only 38 per cent were in males. Of twenty-nine cases in which the side was indicated, twenty-five occurred on the left side of the body.

The author has collected seventy-two reported cases of ganglioneuromata. Thirteen of these were in the region of the central nervous system (three in the cerebrum, two in the cerebellum, two in the tuber cinereum, one in the medulla, one in the Gasserian ganglion, one in the pineal body, two in the dura and ependyma, and one in the spinal canal); thirteen in the medulla of the suprarenal gland; seven in the cervical sympahetic chain; ten in the thoracic sympathetic chain; sixteen in the abdominal sympathetic chain; three in the pelvis; two in the subcutaneous tissues; one in the eyelid; one in the nares; one in the sacral region; one in the chin; one in the knee-joint; one in the sphenomaxillary fossa; one in the mesentery; and one in the lumbar region.

Ganglioneuromata produce relatively few symptoms and are often found in the course of some secondary condition. They sometimes cause paralysis by pressure. Thus de Quervain (72) noted ptosis and

anisocoria in a cervical case, and Busse (14) has described Kredel's case in which a similar tumor in the lumbar region produced paralysis of the leg, bladder and rectum. Occasionally, as in Loretz's case (45), a tumor springing from the gray ramus, may extend through the intervertebral foramina, producing pressure on the cord or cauda equina, and at the same time assuming similar proportions retroperitoneally or behind the pleura. These tumors are usually called hour-glass tumors. Heuer (30) has collected five such cases in which the first symptoms were due to the pressure of the tumor on the spinal cord.

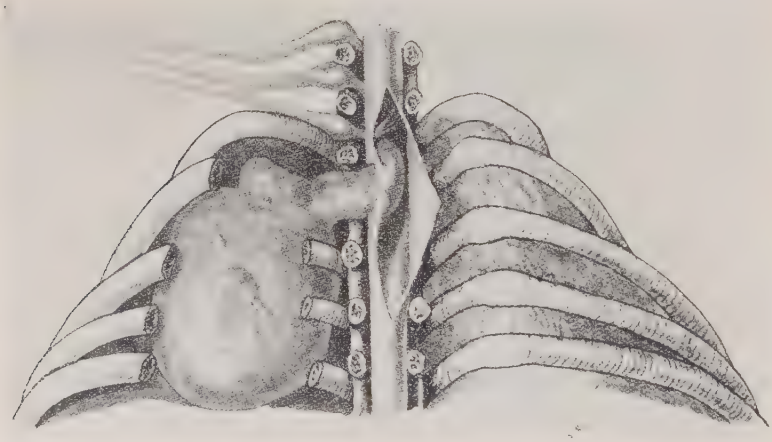

Fig. 162. Hour-glass tumor involving the spinal cord. Several tumors of this description have been ganglioneuromata. (Borchardt (9), p. 640.)

Since these tumors produce no intrinsically characteristic symptoms it can be readily understood why a definite diagnosis has never been made in the absence of histological examination. Pressure symptoms attributable to the autonomic nervous system should suggest such a diagnosis; but since so many other and more common lesions may produce sympathetic paralysis, such evidence is only contributory. Of twenty cases operated upon, seventeen were cured at the time of the last report, while only three died, two from the direct effects of the operation and one from malignant changes in the tumor, due to metastases. In contrast to the neuroblastomata, therefore, the ganglioneuromata are quite benign in their course and offer a relatively good prognosis.

PARAGANGLIOMA

While one branch of the neuroblast tree gives rise to the sympathetic ganglion-cells, the other differentiates into the cells which, by virtue of their chemical affinity with the salts of chromium, are spoken of as chromaffin cells. To the organs composed of chromaffin tissue, the name of paraganglia, has been given by Kohn (37); hence neoplasms of this tissue are called paragangliomata (Alezais and Peyron (1, 2)). The author has collected the reports of four hundred and seventy-seven paragangliomata. Three hundred and twenty-six of these were in the appendix; one hundred and eleven in the carotid body; seventeen in the suprarenal gland; fifteen in the small intestine; four in the abdominal sympathetic chain; one in the aortic ganglion; one in the retroperitoneal tissue; and two in the upper pole of the kidney (possibly in the suprarenal gland). While, theoretically, paragangliomata may arise from any of the collections of chromaffin tissue, the greater number, by far, arise in the suprarenal medulla, the carotid gland, and the *gelben Zellen* of the gastro-intestinal tract. On account of their clinical importance these three groups will be considered in greater detail.

Suprarenal Gland

The paragangliomata of the suprarenal medulla are relatively rare; only about seventeen cases have been recorded since the first one was reported (7) by Berdez in 1892. All the reported cases have been quite benign and symptomless, being for the most part autopsy curiosities. As a rule, the tumors are small, varying from the size of a pinhead to aggregations a few centimeters in diameter. In the gross the tumor appears as an enlargement of the suprarenal gland, which on section, is seen to be due to a brownish-gray mass distending the cortex. Microscopically, the tumors are composed of epithelial cells which are arranged in cords along delicately anastomosing capillaries and which, when stained with chromium salts, take a brownish color.

In certain cases, notably those reported by Hedinger (28), Manasse (51), Marchetti (54), Suzuki (84) and Zeckwer (87), sympathetic ganglion-cells and their less mature precursors have been found in the tumors. In each of these cases, the tumor was invading the cortex in a way which would indicate at least potential malignancy. The association of paraganglioma of the adrenal medulla with neurofibromatosis in fourteen reported instances (Herxheimer (29), Kawa-

shima (35), Suzuki (84) and Zeckwer (87)), is an interesting clinical observation.

Carotid Body

More numerous and far more important from the surgical standpoint are the paragangliomata of the carotid gland (Reid (75)). Marchand (52), in 1891, was the first to call attention to this tumor, while Paltauf (68), in 1892, noted four additional cases and, through

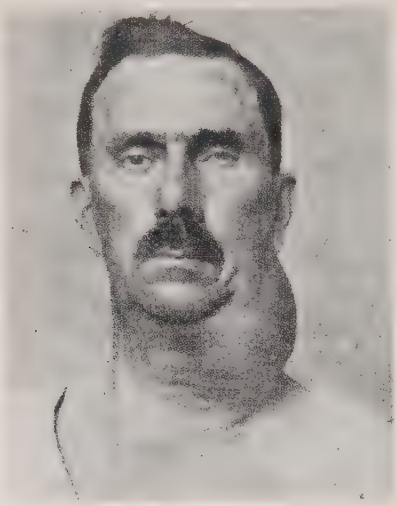

Fig. 163. Paraganglioma of the carotid body (carotid body tumor). Duration of tumor eleven years. A diagnosis of carotid aneurysm was made six years before the removal of the tumor.

his paper, established the condition as a clinical entity. Other instances have been reported by Fedeli (21), Lund (46), Sullivan and Frazier (83). A survey of the literature reveals one hundred and eleven reported cases. Tumors of the carotid gland are usually found in adult life. The average age is forty-one years, with the extremes in age of seven and seventy-four years. Only six such tumors have been reported in patients under twenty years of age. In most instances the tumor had been present for some time before operation; in only fourtween instances had it been observed for less than one year; and in almost 60 per cent of the cases, a mass had been noted for more than

three years. Three patients dated the appearance of the swelling from a time over thirty years previous to operation. In many of the cases, however, in which the tumor had been evident for more than a year or so, a more rapid growth during the months preceding operation had occurred.

Fig. 164. Carotid body tumor removed from the patient shown in Fig. 163.

For the most part the growth of the tumor is symptomless until the mass begins to cause pressure on the surrounding nerves or upon the pharynx or esophagus. Relatively small tumors may press upon certain nerves. The vagus nerve has been the one most commonly involved (fourteen times); the hypoglossal nerve next (seven times);

and the spinal accessory nerve (twice). In some instances the patient may complain of pain in the throat, ear or base of the skull. Possibly there may be atrophy of the corresponding half of the tongue, or dysphagia may occur. The latter symptom may be due to the protrusion of the growth into the pharynx. Pressure upon the sympathetic chain may also give rise to anisocoria or enophthalmos. In

Fig. 165. Histological section of the carotid body tumor shown in Fig. 164.

a few instances the pressure from large tumors has been known to cause aphonia and dyspnea. Occasionally patients have had a distinct icteroid or lemon tint in the color of the skin.

Tumors of the carotid body have been variously regarded as peritheliomata, endotheliomata, epitheliomata, perithelial angiosarcomata or adenomata, according to the slight variations in the histo-

logical structure. However, while hyperplasia or neoplastic growth of the structural elements of the carotid body aside from the chromaffin tissue does occur, the behavior of these tumors and the general similarity of their gross and histological appearance would seem to indicate that in most carotid body tumors, there is a definite pathological entity. Certain cases, notably two of those reported by Gilford (23) seem to have been sarcomata; while another case mentioned by him, was probably a carcinoma. Grossly, these tumors appear as nodular masses which are of firm consistency and even texture, characteristics which prompted the suggestion of the appellation of "potato tumors" by Gilford. On section, they are usually well encapsulated with fibrous tissue and the cut surface usually presents a yellow or orange color, varying to red with the vascularity of the tumor. In many instances, the great vascularity has suggested angiosarcoma or even aneurism. The adjacent lymph-nodes are occasionally agglomerated with the tumor but are rarely involved by the growth.

Histologically, an alveolar topography is quite characteristic, the growth being composed of polyhedral granular cells arranged in compact groups and surrounded by hyperplastic capillary endothelium. The amount of stroma varies but is often scanty, the characteristic cells being in intimate contact with the capillary endothelium. Because of the site of the carotid gland, tumors arising from it present a rather definite clinical picture. Furthermore, important neighboring structures so soon become involved that the surgical attack furnishes a very difficult problem.

Keen and Funke (36), in writing of these tumors, mention the following points which may aid in the diagnosis: (*a*) position at the bifurcation of the carotid artery; (*b*) movability lateral, but not vertical; (*c*) ovoid shape; (*d*) smooth and not lobulated; (*e*) single; (*f*) transmitted pulsation; (*g*) bruit and thrill; (*h*) bulging of the wall of the pharynx; (*i*) occasional constriction of the pupils; (*j*) slow growth; (*k*) long duration; (*l*) a rather firm elastic consistency. From the negative standpoint they are: (*a*) not tender; (*b*) not painful; and (*c*) the deformity is the main complaint.

The position of the artery in these cases deserves further comment. Whereas other cervical growths may dislocate the artery, they usually leave it freely movable. In carotid body tumors the carotid artery is caught, fixed and carried lateralwards so that it lies in a groove on the

lateral or anterolateral aspects of the tumor. Since many of these tumors are extremely vascular, a palpable pulsation and associated bruit are frequently evident. These signs have been commented upon in twenty-two cases.

The surgical removal of carotid body tumors is fraught with considerable danger and difficulty, because the frequent involvement of the carotid artery in the substance of the growth necessitates the ligation or excision of this vessel or even the entire neurovascular bundle. Of forty-three cases in which it was necessary to ligate the carotid artery, nineteen, or 44 per cent, died. In addition, two other patients suffered hemiplegia. The concomitant ligation of the com-

Fig. 166. Paragangioma of the carotid gland and the location of the tumor with respect to the carotid artery. (Keen (36), p. 475.)

mon carotid artery and internal jugular vein in fifteen cases was attended with a mortality of 54 per cent. The mortality in the collected cases was about 40 per cent, certainly a high rate for an operation performed in the greater number of instances for cosmetic reasons. Such considerations have led several surgeons—Da Costa (17), Reclus (74) and others—to advise against operation in the simple cases where a definite diagnosis has not been made prior to the fixation and involvement of the neurovascular bundle.

Appendix

In 1907, Oberndorfer (66) distinguished from the true carcinomata of the gastro-intestinal tract, a group of neoplasms to which he applied

the name of carcinoid tumors. These, according to the present author's classification, are called paragangliomata. Huebschmann (32), in 1910, suggested that these tumors had their origin in the so-called *gelben Zellen* of the crypts of Lieberkühn, the chromaffin character of which had been proven by Schmidt (79) in 1905. Several years later Gosset and Masson (25) studied these cells and the carcinoid tumors. They concluded that the tumor-cells are probably identical with the chromaffin tissue of the paraganglia. While the idea of the origin of the carcinoid tumors from chromaffin tissue has not been universally accepted, the findings of Gosset and Masson have been confirmed by other authors, notably by Hasegawa (26, 27),

Fig. 167. Carcinoid tumor (paraganglioma) of the appendix.

Danisch (18), and Forbus (22); and the weight of evidence seems to point to an endocrine origin. As such, they deserve consideration among the tumors of tissue related to the vegetative nervous system.[2]

Pathologically, these tumors appear as single or multinodular enlargements; they occur most commonly in the appendix and ileum, although they are also found elsewhere in the gastro-intestinal tract.

[2] P. Masson has recently (63) given very strong evidence that these pigmented cells have their origin from the entoderm. He has observed, in embryos, the budding of these cells from the tip of the intestinal glands. He has also demonstrated these cells in the neuromata of appendices.

Occasionally they resemble a bulbous enlargement of the distal portion of the appendix. The incidence of their occurrence in appendices removed at operation is estimated at 0.4 per cent. The tumors are usually found in the submucosa but they may extend into the muscularis or more rarely into the mesentery. Microscopically they are

Fig. 168. Submucous carcinoid tumor of the appendix. The tumor contains a great deal of fibrous (or nervous, according to Masson (63)) tissue. The lumen is almost obliterated. (Stain: hematoxylin and eosin.)

made up of rather round, oval or low cylindrical cells with round or oval nuclei, which stain quite deeply but do not exhibit much variation in size or many mitotic figures. These cells are found in nests or alveoli, surrounded by interlacing trabeculae of fibrous or smooth muscle-tissue. Because of the peculiar ability of certain of the cells

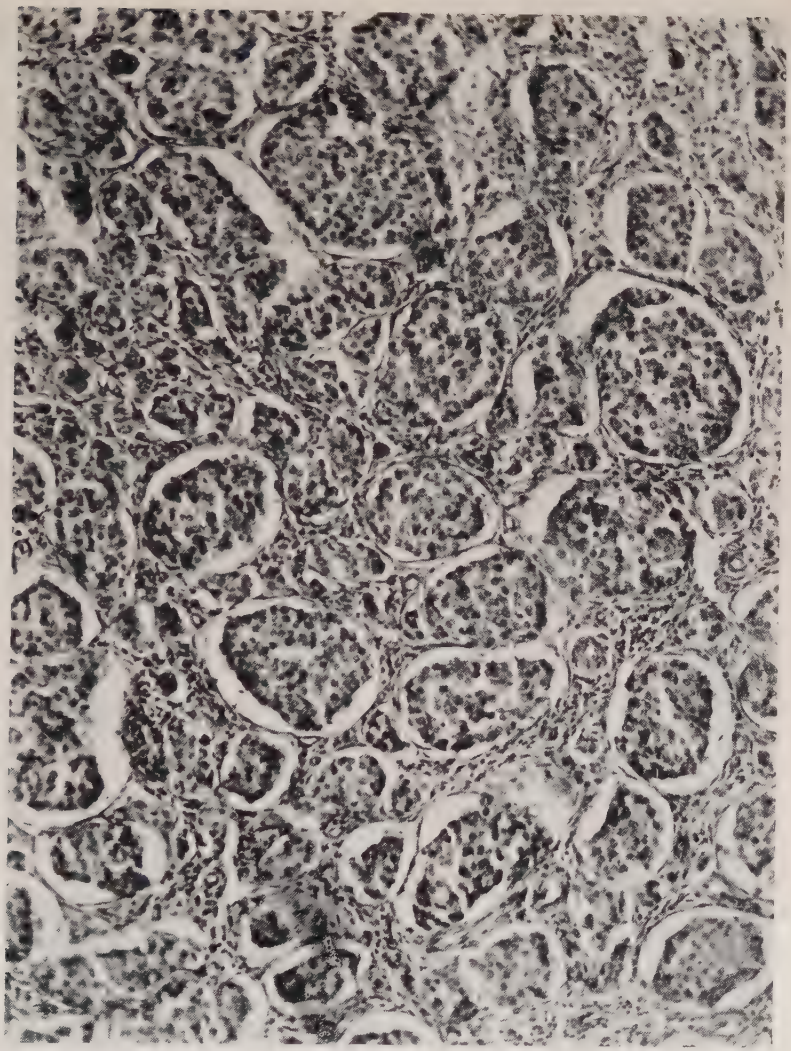

FIG. 169. Carcinoid tumor of the appendix. Low-power magnification. Note the similarity to Fig. 165.

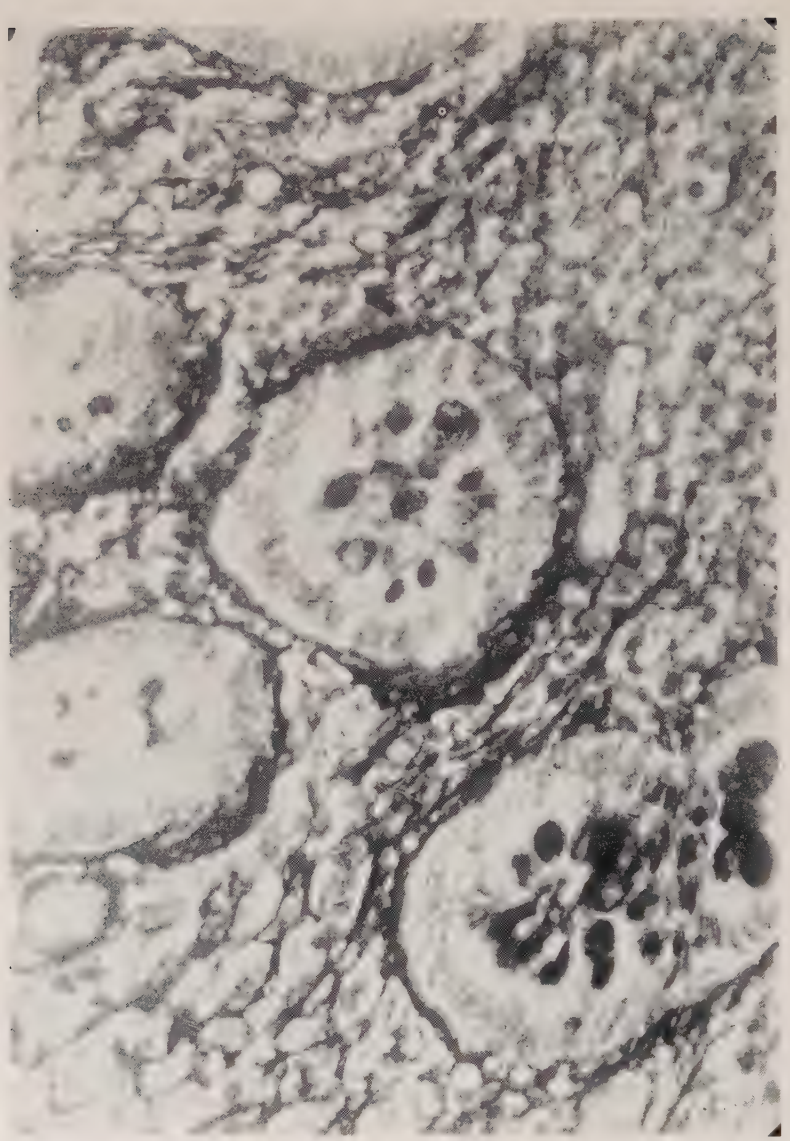

FIG. 170. Argentaffine cells in a carcinoid tumor of the appendix. (Silver stained, and counterstained with hematoxylin—van Gieson.)

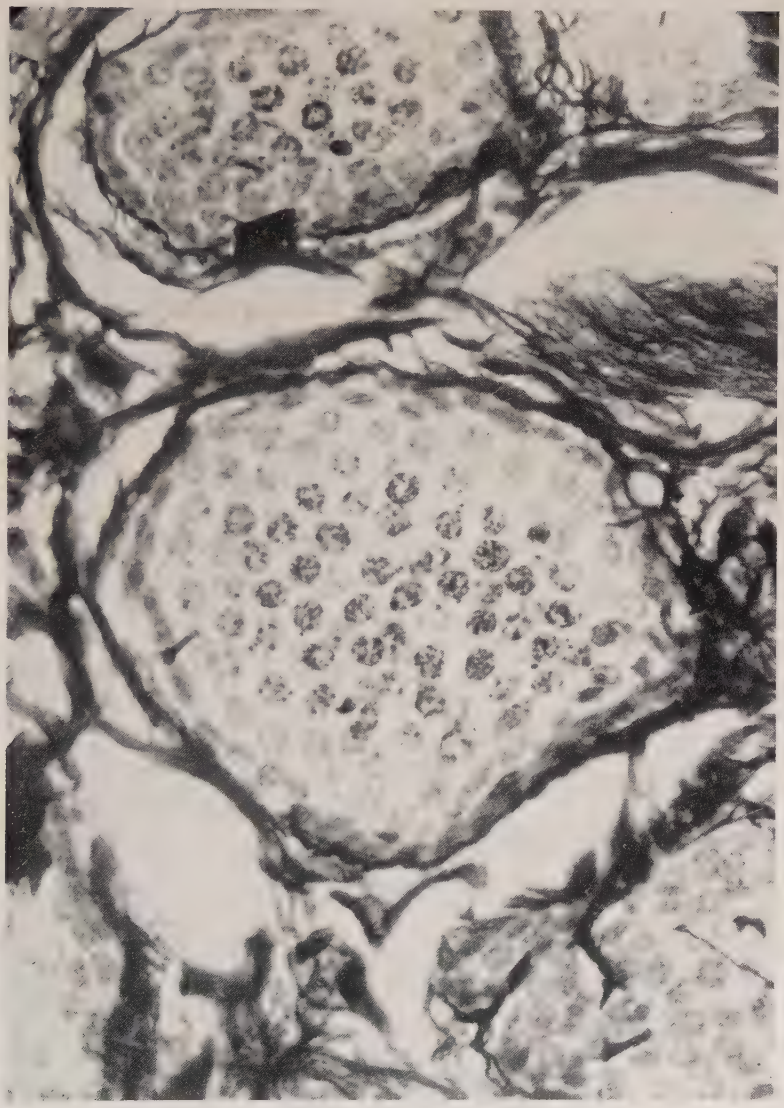

FIG. 171. Nests of argentaffine cells in a carcinoid tumor of the appendix. (Silver stained, and counterstained with hematoxylin—van Gieson.)

to reduce silver from ammoniacal solution, the name of argentaffine tumors has been suggested. Clinically, these tumors are quite benign and seldom, if ever, produce symptoms of themselves. In many of the cases the tumor has been found in appendices which were incidentally removed in the performance of other abdominal operations. No doubt many of these tumors have been entirely overlooked inasmuch as they may be present without giving any evidence externally in the appendix.

In reviewing the literature, the author has found twenty-five cases in which the appendiceal growth was definitely a carcinoma, some of which were of the colloid type. At the Mayo Clinic the incidence of appendiceal tumors was 0.44 per cent among the first 5000 cases of appendectomy reported; 0.6 per cent among the next 3039 cases (MacCarty (47), MacCarty and McGrath (48–50)). One case of the sixty-four appendiceal tumors reported from this clinic was definitely malignant. Stewart and Taylor (81) mention a "carcinoid" tumor of the appendix that caused a metastatic nodule in the pelvis, and claim to have found in the literature seventeen cases of "carcinoid" tumors associated with metastases. The author agrees with Forbus who doubts whether true paragangliomata of the appendix and gastro-intestinal tract ever metastasize. The latter writer has called attention to a peculiar adenocarcinoma which superficially resembles "carcinoid" tumors but does not give any of the characteristic chemical or staining reactions. It will, however, produce extensive metastases.

NEUROMA

Neuromata may develop in the sympathetic nerves as well as in the peripheral nerves. De Massary and Walser (55) have reported a case of a tumor in the wall of the stomach, which they considered was derived from Schwann's syncyticum, and because of the identity of this tissue with the central neuroglia, they regarded it as a glioma. The neuromata of the sympathetic nerves have been studied by Masson (56), and the embryonal sympathomata have been described by Quirin (73). Both these classes of neoplasms appear as non-malignant tumors, which occur more commonly in the uterus than in other viscera.

Careful study by Masson (57–62) and by Askanazy (4) of the proliferation of the nerve-elements around the margins of gastric ulcers

and in the walls of previously inflamed appendices—particularly those of the chronic obliterative type—has convinced these authors that, in some instances, such an overgrowth may reach a true neoplastic grade. Dupuy (20) has described a case of ulceration and chronic perforation of the gastric wall, in which there was a considerable hyperplasia of the cells and fibers composing Auerbach's plexus. Leriche (42–44) and others, who have performed a periarterial sympathectomy on the iliac arteries or upon the abdominal aorta, for intractable pelvic pain, base the rationale of the operation upon the idea that the pain is caused by neuromata formed in connection with the pelvic or uterine nerves—such as have been demonstrated in the uterus by Masson.

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Section VI

THERAPY

CHAPTER XXXIII

PHYSIOLOGIC EFFECTS OF THORACIC AND LUMBAR SYMPATHETIC GANGLIONECTOMY OR TRUNK-SECTION[1]

GEORGE E. BROWN, M.D., AND ALFRED W. ADSON, M.D.

THE permanent vasomotor and other physiologic changes resulting from sympathetic lumbar ganglionectomy with ramisectomy or trunk-section have stimulated investigation and clinical application. The authors first studied a group of patients with spastic paralysis and subsequently a group with vascular disturbances of the vasoconstrictor types, that is, Raynaud's disease, and such other vascular diseases as thrombo-angiitis obliterans, scleroderma, and one case of subacute polyarthritis. This report includes the pre-operative and postoperative physiologic studies on a total of thirty-nine cases.

ANATOMY AND PHYSIOLOGY

Ranson (51) has summarized the anatomy of the sympathetic nervous system as follows:

> The sympathetic nervous system is an aggregation of ganglia, nerves, and plexuses through which the viscera, glands, heart, blood-vessels and smooth muscle in other situations receive their innervation. The most conspicuous feature of the system is a pair of ganglionated nerve-cords or sympathetic trunks, which extend vertically through the neck, thorax, and abdomen. Each sympathetic trunk is composed of a series of ganglia bound together by short nerve-strands. Every spinal nerve is connected with the sympathetic trunk of its own side by one or more gray rami communicantes through which it receives sympathetic fibers for the control of blood-vessels, sweat-glands and smooth muscles of the hair follicles situated within the territory of its distribution. The majority of the nerve-fibers that take origin in the ganglia of the sympathetic chain are distributed through the gray rami and the spinal nerves.

The ganglia of the lower thoracic and abdominal portions of the chain are less concerned with visceral activity than with constriction

[1] From the Division of Medicine and the Section on Neurologic Surgery, The Mayo Clinic, Rochester, Minnesota.

of the peripheral blood-vessels, erection of the hairs, and secretory activity of the sweat-glands. But the upper thoracic and cervical ganglia bear a more intimate relation to the thoracic viscera, since they contain the cells of origin of postganglionic fibers for these viscera.

Ranson continued:

The thoracic and upper lumbar nerves are connected with the sympathetic chain by white as well as gray rami communicantes. These white rami contain both afferent and efferent fibers. The latter take origin from cells in the gray matter of the spinal cord, travel through the ventral root and white rami, and enter the sympathetic system, to terminate in synaptic relation with the nerve-cells found in the sympathetic ganglion. They are often designated as preganglionic fibers, while those that arise in the ganglia and relay the impulses onward are called postganglionic. The gray rami contain postganglionic fibers; the white rami contain preganglionic fibers.

The majority of the preganglionic fibers turn either upward or downward in the sympathetic chain, and run for varying distances within it before ending in its ganglia. The cervical sympathetic trunk is composed exclusively of preganglionic efferent fibers, derived through the white rami from the upper thoracic nerves and ascending to terminate in the cervical sympathetic ganglia. The lumbar and sacral portions of the trunk are composed in the major part of descending fibers derived through the white rami from the lower thoracic and upper lumbar spinal nerves.

Those fibers of the white rami, which are concerned with the innervation of the abdominal viscera, pass into the splanchnic nerves and end in the celiac ganglion. These fibers reach the splanchnic nerves after passing through the lower half of the thoracic sympathetic chain; but they are not interrupted in the chain-ganglia through which they pass.

The sympathetic nervous system receives additional fibers from the spinal cord by way of the visceral branches of the second, third, and fourth sacral nerves, and from the brain through certain of the cranial nerves.

There are, then, these three streams of preganglionic visceral efferent fibers: (*a*) the cranial stream from the third, seventh, ninth and tenth cranial nerves; (*b*) the thoracicolumbar stream, from the thoracic and upper lumbar spinal nerves by way of the white rami; and (*c*) the sacral stream from the second, third, and fourth sacral nerves. The cranial and sacral streams belong to what is commonly called the parasympathetic system.

Most of the sympathetic nerves contain, in addition to the fibers already discussed, also sensory fibers, which convey impulses from the viscera to the spinal cord. These sensory fibers have their cells of origin in the spinal ganglion and reach the sympathetic system by way of the white rami. Visceral reflexes, therefore, travel arcs of at least three neurons each. The impulses reach the spinal cord along visceral afferent fibers in the dorsal root and leave along preganglionic visceral efferent fibers in the ventral roots and white rami. These fibers end in sympathetic ganglia, and the impulses which they carry are relayed to involuntary

muscle and glandular tissue by postganglionic fibers. The ganglia of the sympathetic trunk do not serve as reflex centres but only as relay stations in the conduction pathways from the spinal cord to the viscera.

The vasoconstrictor fibers arise in the central nervous system and leave the spinal cord as preganglionic fibers from the second thoracic to the second lumbar ganglion. These fibers are mixed with other autonomic fibers such as sweat-fibers, pilomotor fibers, oculopupillary fibers and accelerator fibers to the heart. They reach the sympathetic chain from the anterior roots by way of the rami communicantes. They end in one or the other of the ganglia, then leave as postganglionic fibers. Those fibers which supply the skin of the extremities communicate with the corresponding spinal nerve by way of the gray rami. Their distribution peripherally is that of the spinal nerve. Vasodilator fibers have not been demonstrated for all regions of the body. From the thoracic portion of the sympathetic system vasodilator fibers pass to the limbs by way of the branches of brachial and lumbar plexuses, but as Howell states (27), the exact course of these fibers is not as yet entirely settled. Their origin from the sympathetic chain has not been demonstrated in the nerves of the limbs. They may follow the vasoconstrictors, or, as Bayliss' work seems to show (6), vasodilator effects occur in afferent fibers which have the so-called antidromic action. The vasoconstrictor fibers for the limbs probably are distributed chiefly to the skin. Section of these fibers produces dilator effects, exerted largely in the arterioles. The skeletal muscles of the limbs, according to Gaskell (20), receive both dilator and constrictor vasomotor fibers; the former, however, predominate. Metabolic substances play a rôle in producing vasodilatation in the muscles.

The caliber of the blood-vessels is under a dual control: (*a*) The vasomotor fibers maintain the small arteries in a condition of tonus. (*b*) After complete denervation of the arteries there is also a return of tonus, which as was shown long ago by Goltz and Ewald (22) is capable of inducing variations in the caliber of the vessel-wall.

As Howell has stated (27), there is an increased amount of evidence showing that the capillaries and veins are not fixed systems, and that they are also under the influence of local, chemical or special nerve-fibers. Such fibers have been demonstrated for the portal and mesenteric veins. Krogh's (39) investigations on the capillaries of the frog show that these vessels receive vasoconstrictor fibers from the sym-

pathetic system, thus maintaining the capillaries in a state of tonic contraction. According to Krogh, the vasomotor effects on the capillaries are exerted through Rouget cells; there is no conclusive proof of the existence of these cells in the capillaries of the human being. The effects of metabolites of the acid type and of histamine, in producing capillary dilatation, seem to be well established.

DEVELOPMENT OF SURGICAL METHODS

Periarterial sympathectomy was suggested by Jaboulay (1898) for trophic and gangrenous diseases of the extremities (31), but it was not until 1913 when Leriche became interested in this field that the operation gained any prominence (46). Due to Leriche's enthusiasm, many physicians and surgeons have employed the procedure and have given varying reports on its success and failure. The hyperemia that developed following periarterial sympathectomy was at first explained on the ground that the vasomotor fibers were centrifugal in distribution and consequently were sectioned during the periarterial sympathectomy. However, it was learned that similar hyperemia occurred on the opposite side, on which no operation had not been performed. This gave rise to the belief that the hyperemia was more active than passive and that it resulted from the sectioning of the centripetal ascending fibers.

The anatomical work of Kramer and Todd (38) and of Potts (50) on the innervation of the vessels of the extremities, proved that with the exception of the subclavian and femoral arteries, which received sympathetic vasomotor fibers directly from the ganglia, the vasomotor innervation of the arteries and arterioles corresponded to the innervation of the somatic segments. Even though Leriche and Fontaine (48) have not been able to present anatomical proof, they still hold that there must exist some intramural nerve-centres in the arterial wall.

The present authors have observed hyperthermia of the extremities in normal individuals, in cases of Raynaud's disease and in thromboangiitis obliterans, following the febrile reaction after the intravenous injection of foreign protein; this may persist for several days. In some individuals the reaction is so pronounced that injections of protein are prescribed as a therapeutic measure. It has also been observed that following the administration of a general anesthetic to patients suffering from vasoconstrictor disturbances there occur hy-

peremia and increased surface temperature in extremities on which operation has not been performed. It is the authors' belief that these temporarily increased changes in blood-flow which result from the administration of protein are due to the heat-regulating mechanism which attempts to dispose of the increased body-temperature and, further, that these temporary hyperthermic changes arising from periarterial sympathetomy, incomplete ramisectomy, or ganglionectomy may be due to increased systemic temperatures following surgical procedures but that they are more likely to be due to incomplete interruption of vasoconstrictor fibers. The more complete the division of the postganglionic vasoconstrictor fibers, the more complete and permanent will be the results of the operation. In Raynaud's disease, this fact is evidenced by the disappearance of the cyanosis and pain and permanently increased vasodilatation of the peripheral part, with the production of a warm, comfortable, normal appearance of the hands and feet.

The work of Leriche and his followers has stimulated many surgeons to develop operative measures of a greater scope in an attempt to paralyze permanently the vasoconstrictor nerves before they re-enter the spinal nerves to be distributed to the arteries and arterioles. These operations have consisted of ganglionectomy, ramisection and section of the trunk. Jonnesco (34) was one of the first to advocate resection of the stellate[2] ganglion (lower cervical and first thoracic ganglia) for angina pectoris; but Brüning (11), Hunter (29), Royle (55), Brown and Adson (10), Diez (16), and Davis and Kanavel (15), have been responsible for the renewal of interest in the surgical possibilities in the treatment of vascular diseases of the vasoconstrictor type.

Royle (55), in his report of January 26, 1924 on the treatment of spastic paralysis by sympathetic ramisection, made the following comment, upon examining a patient six hours after operation: he noticed that the right leg, on the affected side, was brighter in color than the left, that it felt warmer and gave evidence of capillary dilatation

[2] A question has been raised in regard to the use of the term "stellate" to indicate the lower cervical and first thoracic ganglia in the human being. Dr. Charles W. Greene (23) believes that the use of the word stellate should be confined to the lower animals in which the lower cervical and first thoracic ganglia are frequently fused; this fusion is not usual in human beings. Common usage by many workers, however, has led to the continued use of the term "stellate ganglion."

though he was unable to demonstrate any difference in temperature with an ordinary clinical thermometer.

Ever since May 20, 1924, the date of their first abdominal transperitoneal lumbar sympathetic ganglionectomy for spastic paralysis, the present authors have observed marked hyperthermia which they have verified by accurate quantitative studies. When it became evident that the surface temperature of the feet remained elevated for months and gave evidence that it would remain so permanently, they concluded that they would be justified in attempting the procedure in a patient with Raynaud's disease. This was done on March 19, 1925, and the operation was reported on June 20, 1925 (2). The relief from symptoms in that instance was incredibly dramatic. This patient, and others upon whom lumbar sympathetic ganglionectomy was performed for Raynaud's disease, have continued to be relieved following operation. The authors can confidently say, therefore, that the disease as it affected the lower extremities was completely cured.

Before proceeding with the description of the surgical technique used by one of the authors (Adson), it might be of interest to review briefly the history of cervicothoracic ganglionectomy as carried out through the anterior approach.

Jonnesco (33) called attention to the fact that the operation, resection of the stellate ganglion, with or without resection of the middle and upper cervical ganglia was first performed in 1896 for epilepsy and exophthalmic goitre; later, by other surgeons, for migraine and glaucoma. Jonnesco (34) followed a suggestion made by François-Franck (19) and performed his operation for the relief of angina pectoris. From that period until recently it has been used by scores of surgeons for almost every conceivable ailment of the head, neck, and upper extremities. The frequent alleviation of angina pectoris by resection of the cervicothoracic ganglia has justified the method. The character of the present discussion does not permit a review of the surgery of angina pectoris. In 1923 Brüning (12) resected the cervicothoracic ganglia by the anterior approach for Raynaud's disease and for scleroderma. Davis and Kanavel (15) in 1926 carried out a similar procedure for Raynaud's disease of the upper extremities, with partial relief of the vasospastic disturbance.

In 1924, Royle (54) modified the Jonnesco operation, suggesting ganglionectomy and section of the trunk below the first thoracic ganglion by the anterior approach. The present authors believe that his

latest suggestion has offered the best anterior approach to the cervicothoracic ganglia. They agree with Royle also in his statement that operation in this surgical field is fraught with dangers and that previous failures were due to incomplete operations. They disagree with him as to sectioning the thoracic trunk below the stellate ganglion, for Kuntz has shown that the second thoracic ganglion contributes gray fibers to the first thoracic spinal nerve, as well as to the second thoracic spinal nerve which often contributes to the lower trunk of the brachial plexus. Through the posterior intrathoracic approach, the authors have been able at operation to substantiate Kuntz's observations (40).

All of these more or less partial or incomplete results in the treatment of vasoconstrictor disturbances of the upper extremities by resection of the so-called stellate ganglion furnished convincing proof that some other approach was necessary. Therefore, the problem was to find a procedure that would permit complete removal of the first and second dorsal and lower cervical sympathetic ganglia and the intervening trunk, in order to break completely all sympathetic fibers to the subclavian and axillary arteries and to the brachial plexus. It appeared that the posterior approach was the logical procedure and this was the method believed necessary when the first attempt failed to relieve Raynaud's disease of the upper extremities by the anterior approach. The rami from the ninth, tenth, eleventh and twelfth dorsal ganglia had been sectioned through a dorsal approach for a neuropathic condition of the abdomen by von Gaza (21) in 1924. In searching the medical literature for information concerning the exact anatomy of this field, the author's attention was called to an essay by Henry on an anatomical dissection of the cervicodorsal ganglion from the posterior approach (24). This evidence was convincing that it was possible to resect the second thoracic ganglion, the cervicothoracic and the intervening sympathetic trunk and thus completely interrupt all of the efferent fibers to the vessels of the arm as well as those to the head and neck. In the first case the procedure was divided into two operations: resection of the second thoracic ganglion, the cervicothoracic ganglion and the intervening sympathetic trunk on the right side was performed July 31, 1928; and a similar operation was carried out on the left side, September 11, 1928 (3).

Inasmuch as it was necessary to perform bilateral operations, Henry's (24) suggestions concerning skin and muscle flaps had to be modified. Furthermore, since it was believed essential to include the

second thoracic ganglia and rami, on account of Kuntz's (40) suggestion regarding the anatomy, it was also necessary to enlarge the scope of the operation to break all afferent impulses from the heart to the thoracic nerves. Only in this way could it be expected to relieve all of the referred pain to the arms and thoracic wall. Cannon (13) has shown that sensations of pain travel over afferent fibers to one or all of the five upper dorsal nerves.

SURGICAL TECHNIQUE

Removal of the Lumbar Ganglia

The incision for approach to the lumbar ganglia is made from the symphysis to a point from 5 to 7 cm. above the umbilicus, between the rectus abdominis muscles and to one side of the umbilicus. The sheaths of the rectus muscles subsequently are opened on each side below the umbilicus and, on the left side, above the umbilicus, facilitating closure along anatomic lines. If the abdomen is extremely flaccid, it may be advisable to make an overlapping closure (C. H. Mayo type) in the external leaves of the fascia of the rectus abdominis muscles. Before the peritoneum is opened, the patient is lowered from the horizontal position to the Trendelenburg position, thus insuring better exposure of the lumbar sympathetic ganglia. Although general exploration may reveal other abdominal lesions, they are not disturbed at this time since it is not advisable to run the additional risk of contamination. The intestines are packed upward, as is done in performing hysterectomy. It is immaterial whether one approaches the ganglia first on the right or first on the left side. Usually, the ganglia on the right side are more difficult to reach because of the intervertebral veins which run anteriorly and across the sympathetic trunk. It is also more difficult to elevate the inferior vena cava on the right than the abdominal aorta and the common iliac artery on the left.

In exposing the left lumbar sympathetic chain, it is necessary to loosen and elevate the sigmoid and the lower portion of the descending colon. This is done by incising the peritoneum superior to, and just lateral to, the anterolateral border of the upper portion of the sigmoid and the attachment of the lower portion of the descending colon. When the line of cleavage is once started, the large bowel, with the posterior wall of the peritoneum, can be elevated readily and retracted beyond the median line, thus exposing the retroperitoneum, the ureter (as it crosses the bifurcation of the common iliac), the left common iliac artery and vein, the lower end of the abdominal aorta, the genitocrural nerve (which perforates the psoas muscle), the psoas muscle, the lumbar vertebrae, the lymph-nodes, and the lumbar sympathetic ganglia, trunk, and rami, which lie on the lumbar vertebrae, just mesial to the psoas muscle. The ureter on the left side is more easily retracted mesially than laterally. By means of a moist sponge it is held gently in a median-line position, together with the colonic mesentery, the upper end of the sigmoid, and the lower end of the descending colon. The abdominal aorta is elevated and retracted mesially by finger-traction on a gauze sponge. It is held by an assistant. The sympathetic ganglia, trunks, and rami are then dissected free by a wet cotton-

ball dissector held in a thumb forceps. It is well to begin at one or the other end of the lumbar sympathetic chain. On the left side, it is preferable to expose the fourth lumbar ganglion at the brim of the pelvis, and divide the sympathetic trunk below it. All of the rami, including those to the spinal nerves, the hypogastric plexuses, and the aortic plexuses, are then divided. The dissection is then carried upwards to include the third and second lumbar ganglia. Undue traction should not be exerted on any of the tissues handled; especially must traction be avoided on the mesentery leading to the sigmoid and colon, in order to avoid the possibility of rupture or thrombosis of arteries or branches of arteries supplying the large bowel.

The approach to the lumbar sympathetic ganglia on the right is similar to that on the left, except that the peritoneal incision is made just lateral to the right lateral border of the abdominal vena cava; the incision then is carried downwards over the right common iliac vein into the true pelvis, upwards and mesially along the root of the mesentery of the small intestine, partially across the vena cava for a distance of 15 cm. from the brim of the pelvis, and downwards into the pelvis for a distance of from 5 to 7 cm. The cecum, the small intestine, and the ureter are retracted outwards and upwards. The vena cava is retracted mesially, and the common iliac vein, downwards and mesially. Just above the brim of the pelvis on the right side, in the posterior wall of the peritoneum, may be encountered several small veins which can be divided and ligated. The further exposure and removal of the lumbar sympathetic ganglia and division of all of the rami and the sympathetic trunk, are similar to the procedures employed on the left side. However, the fourth lumbar sympathetic ganglion on the right side usually lies underneath the intervertebral vein and not superficial thereto, as it does on the left side.

The closure consists in the accurate apposition of both retroperitoneal incisions to prevent retroperitoneal hernia, and the accurate closure of the abdominal wall to prevent postoperative ventral hernia.

Removal of the Upper Thoracic Ganglia

After the patient has been anesthetized, he is placed in the prone position on two soft pillows and the arms are permitted to hang down over the edge of the table to allow the retraction of the scapula outward and forward. The neck is flexed forward and the head is supported by an Adson-Little cerebellar head-rest. The incision in the skin is made in the median line, from the tip of the sixth cervical spine to the tip of the fourth thoracic spine. The incision is then carried down to the spinous processes, exposing the fascia over the trapezius muscle on both sides. The fascia-muscle incision is made on each side and parallel with the spinous processes, extending from the seventh cervical vertebra to the fourth thoracic vertebra. The procedure at this point is carried to completion on one side before the muscular dissection on the opposite side is begun. The fascia-muscle incision is made first through the tendinous attachment of the trapezius to the spinous processes, and subsequently through the spinous attachment of the rhomboids and serratus posterior muscle. Then a retractor exposes the erector spinae group of muscles and the lower end of the splenius cervicis. The transverse processes of the thoracic vertebrae can be palpated through these muscles after it is certain that the spinous process of the second dorsal vertebra has been identified, as well as the tip of the

transverse process of the second dorsal vertebra. Blunt dissection is made through the erector spinae group, parallel with the spinous processes. The retractor is replaced at a deeper level and opposite the transverse process of the second dorsal vertebra. Muscular attachments to the transverse process are now freed mesially until one can demonstrate the process where it fuses with the body and the lamina. The periosteum of the rib is incised on its dorsal aspect. This permits the exposure of the rib lateral to the transverse process for a distance of 3 cm. The rib is cut at the outer border of this area of exposure and the transverse process is cut where it joins the body of the vertebra. Occasionally one may have difficulty with the intercostal artery, but this can be ligated, care being taken not to injure the first or second thoracic nerves. The pleura and lung are now gently dissected from the lateral side of the vertebra and are retracted anteriorly and laterally. This procedure, in turn, will expose the sympathetic trunk between the second thoracic and the cervicothoracic sympathetic ganglia; the trunk lies at a level corresponding to the articulation of the head of the second rib. After exposure of the sympathetic trunk, the procedure consists in the dissection and the removal of these ganglia and the intervening trunk, elevating and resecting the second thoracic ganglion, dividing any gray rami that may run laterally from the second thoracic ganglion to the first thoracic nerve. After the second thoracic ganglion has been elevated and the sympathetic trunk has been divided below, traction on the sympathetic trunk is made from above downwards, thus exposing the cervicothoracic ganglion. This exposure is accomplished by first dividing the ramus of the ansa subclavia and subsequently dividing the rami as they pass off to the first thoracic spinal nerve. These manœuvres permit the gradual mobilization of the ganglia of the thoracic chain and finally the retraction of the cervicothoracic ganglion sufficiently to divide all of the rami ascending from the ganglia into the cervical region.

EFFECTS OF LUMBAR GANGLIONECTOMY

Effects on the Vasomotor Nerves

The vasomotor changes resulting from lumbar ganglionectomy have been studied, first by determining the variations in the surface temperature of the legs and feet by the thermocouples; and second, by ascertaining by means of the Stewart-Kegerreis calorimeter (36, 58), the amount of heat eliminated from the feet. There is, at present, no clinical method for estimating accurately the volume-flow of blood through the limb. The methods available are those which give indirect data on the volume-flow of blood through the part, as shown by Sheard (57). The surface temperature measures the amount of heat in an isolated area of the skin, and gives information largely on the state of the surface vessels. The surface temperature does not give exact information as to the changes occurring in the deeper vessels, although there is a close anatomical relationship between the deep

and the superficial circulation. It is certain that the vasomotor activity manifests itself to a larger degree in the vessels of the skin because of its sensitive heat-regulating mechanism. Likewise, measurements on the rates of heat-loss give data dealing largely with the amount of blood in the surface circulation and with the vasomotor changes occurring in the surface vessels of the entire hand or foot. These methods are of great value for comparative purposes, provided the studies are well controlled and carried out under comparable room or environmental temperature.[3]

Spastic Paraplegia

Included in this group were twelve patients with spastic disturbances in the lower extremities and on whom lumbar ganglionectomy was performed in an attempt to modify the tonus of the muscles of the legs. Surface temperature of the feet in these subjects before operation was not low. The peripheral vessels were patent, and as a rule abnormal or excessive vasoconstrictor activity was absent. The pre-operative surface temperature of the foot varied from 25° to 29°C. (normal values). Table XI indicates the pre-operative and the post-operative surface temperature. Following operation there was an average increase in the surface temperature of the distal portion of the feet of 5.2°C., and in the lower leg of 2°C. The average rate of heat-loss before operation was 0.94 small calory of heat eliminated each minute for each square inch of surface area. Following operation the average value was 2.9 calories, an increase of approximately 300 per cent. These studies were carried out from fifteen to twenty-one days after operation. There were no significant changes in the color of the feet after operation. A total loss of reflex sweating in the feet and lower part of the legs was a constant observation.

Vasospastic Disturbances in the Feet; Raynaud's Disease

This section is based on six cases. Raynaud's disease is a symmetrical vasomotor disturbance of the spastic type, affecting the acral areas and predominantly present in females. It is manifested by intermittent changes in the color and temperature of the extremity affected, with variations in the environmental temperature. The arteries of the extremities are patent; and pulsations are present in those that

[3] Room temperature was maintained at between 23° and 26°C.

are usually palpable. It is an intermittent disturbance since temporary recovery follows exposure of the subject to increased temperature. The temperature of the skin of the extremities is usually low, although subject to wide variations, that is, pecilothermic. The stage of pallor indicates complete constriction of the terminal arterioles, capillaries and small venules (8). The blood ceases to flow through the capillaries, which then become visible owing to the small segments of

TABLE XI

SPASTIC PARAPLEGIA. CHANGES IN SURFACE TEMPERATURE* AND IN THE ELIMINATION OF HEAT AFTER LUMBAR GANGLIONECTOMY

CASE NO.	MAXIMAL INCREASE IN SKIN-TEMPERATURE		HEAT-ELIMINATION, IN SMALL CALORIES, EACH MINUTE FOR EACH SQUARE INCH OF SURFACE AREA	
	Foot	Lower Part of Leg	Before Operation	After Operation
	°C.	°C.		
1		1.5	1.50	3.30
2	2.5	2.0		
3	6.2	3.3	0.30	1.10
4	14.1		0.35	3.90
5	1.1	0.4	1.20	3.00
6	1.6	1.8	0.70	4.10
7	13.8	0.8	0.30	1.40
8	2.0	0.9	0.90	3.50
9	2.4	0.4		
10	4.3	2.7		
11	7.6	0.8	2.25	3.49
12	4.3	7.9		
Average increase....	5.2	2.0	0.94	2.90

* Final recordings made from fifteen to twenty-one days after operation.

static blood retained in them. The degree of constriction and the amount of blood in the exposed capillaries and small venules determine the visible color reaction. In the stage of cyanosis, partial relaxation of the arterioles and venules supervenes; blood is admitted very slowly from the arterioles or by retrograde movement from the venules into the capillaries. The flow is extremely slow and irregular, and cessation is observed for long periods of time. The extremity becomes excessively cold. The rubor or recovery phase, which occurs in some

cases with higher environmental temperature, represents the relaxation of the arteriolar spasm, resumption of capillary flow and transformation of the cyanotic deoxygenated blood into that of the red oxygenated type. The rubor or excessive red color of the extremity is due, then, to abnormally large exposure of red, capillary blood flowing rapidly through an increased number of dilated capillaries and venules. The surface temperature is then high. It would be expected on *a priori* grounds that interference of the vasomotor paths would produce the complete alleviation of this disturbance by preventing the spasm of the small arterioles.

TABLE XII

RAYNAUD'S DISEASE. SUMMARY OF THE CHANGES IN SURFACE TEMPERATURE AND IN THE RATE OF HEAT-ELIMINATION IN THE FEET, FOLLOWING LUMBAR GANGLIONECTOMY

CASE NO.	MAXIMAL INCREASE IN SKIN-TEMPERATURE			HEAT-ELIMINATION, IN SMALL CALORIES, EACH MINUTE FOR EACH SQUARE INCH OF SURFACE AREA	
	Before Operation	After Operation	Increase	Before Operation	After Operation
	°C.	°C.	°C.		
1	31.2	35.5	4.2	0.51	0.85
2	22.1	36.6	14.5	0.44	1.32
3	23.9	36.1	12.2	0.94	1.04
4	22.2	33.2	11.0	1.21	0.69
5	19.9	32.7	12.8	0.23	1.17
6	15.0	33.2	18.2	0.39	1.03
Average values.....			12.1	0.62	1.01

In the group of patients studied the increase in the surface temperature of the distal parts of the feet following lumbar ganglionectomy was very high; the average was 12°C. The pre-operative temperature of the feet was very low, averaging only 22.4°C. under room temperature of 24° to 26°C. Following operation, increases were noted in the rates of heat-elimination, averaging 0.39 calory each minute for each square inch of surface area, or 61 per cent. The relatively moderate increase in heat-elimination in the cases of Raynaud's disease is explained by the fact that many of the pre-operative determinations were made on the extremity during periods when the feet were rela-

tively warm. The increase, and the duration of the increase, in surface temperature are shown graphically in Figure 172.

Residual Vasomotor Activity

The amount of reflex vasomotor activity remaining in the arteries after operation, as studied by variations in the surface temperature, has been determined in several cases of Raynaud's disease (Fig. 172).

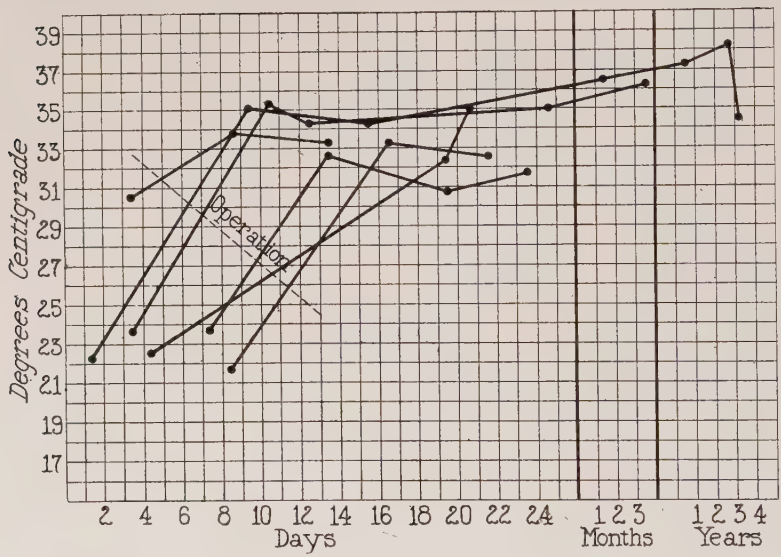

FIG. 172. Graphic representation of surface temperature of the feet before and after lumbar ganglionectomy in Raynaud's disease. The initial point is an average of from two to six readings on different days before operation.

After operation the range was very limited, varying from 1° to 4°C., much less than one would find in a normal subject who had not been subjected to operation. The restricted fluctuation in the surface temperature after operation may be due to the fact that the few vasoconstrictor fibers remaining are sufficient to produce reflex effects; or the fluctuation may be caused by the natural or inherent tonus of the denervated vessels. The latter explanation seems more probable, since with a further lapse of time after operation there has been noticed a further decrease in the degree of the changes occurring in the temperature of the skin. This is probably due to the effects of

atrophy from disuse, which has been demonstrated by Kerper and Collier (37) in the walls of the arteries after lumbar ganglionectomy in animals under experiment.

Thrombo-Angiitis Obliterans

The rationale of carrying out lumbar ganglionectomy in cases of occlusive disease of the arteries affecting the extremities is based on the following clinical and physiological observations: (*a*) In many cases of thrombo-angiitis obliterans, with closure of the main arteries, there are varying degrees of vasospastic disturbance. The color-changes due to lowered environmental temperature are in some cases so striking as to lead frequently to an erroneous diagnosis of Raynaud's disease. This clinical observation gives rise to the conclusion that in some cases the collateral vessels maintaining the circulation of the extremities are subject to excessive vasospastic reactions. This is easily understood if the pathological changes occurring in this disease are recalled, namely, marked inflammatory reaction in all the coats of the arteries, especially in the adventitia or perivascular structures, and cellular thrombosis occluding segments of variable length. Afferent impulses, with the institution of vasoconstrictor reflexes, are undoubtedly initiated by the inflammatory process. (*b*) Further evidence of considerable vasomotor spasm is observed from the calorimetric and thermometric studies carried out on the extremities of some of the patients. The rate of heat-elimination as determined in the hand or foot calorimeter and as measured in the small calories eliminated for each unit of surface area for each unit of time, is subject to variations similar to but less in degree than those observed in normal subjects or in subjects with functional vasospastic disturbances. It was assumed, therefore, that the diminished blood-supply in some cases of thrombo-angiitis obliterans has a twofold basis: occlusion of the main arterial channels, and superimposed vasoconstriction of the collateral circulation.

In order to select the cases suitable for operation on the vasomotor nerves a simple test was devised. The mouth temperature and surface temperature are taken to establish the normal for each patient under conditions of ordinary room temperature. Systemic fever is induced by the intravenous injection of triple typhoid vaccine (9). The mouth temperature and the surface temperature of the affected extremities are then determined simultaneously during the rise and

fall of the fever. In certain cases there are great increases in the surface temperature of the part, with small rises in the systemic temperature. A vasomotor index is determined in the following manner: The rise in the surface temperature minus the rise in systemic temperature represents approximately the temperature change in the skin due to vasomotor effects. This, divided by the increase in the blood

TABLE XIII

THROMBO-ANGIITIS OBLITERANS. CHANGES IN SURFACE TEMPERATURE AND RATE OF HEAT-ELIMINATION IN THE MORE DISEASED EXTREMITY, FOLLOWING LUMBAR GANGLIONECTOMY

CASE NO.	INCREASE IN SURFACE TEMPERATURE IN TOES		HEAT-ELIMINATION, IN SMALL CALORIES, EACH MINUTE FOR EACH SQUARE INCH OF SURFACE AREA	
	Minimal	Maximal	Before Operation	After Operation
	°C.	°C.		
21	4.2	5.0	1.10	5.00
22	0.6	6.0	0.70	1.50
23	0.8	7.6	0.40	0.70
24	1.3	5.3	0.45	0.70
25	2.7	5.6	0.90	1.60
26	2.3	2.3	0.70	0.60
27	4.7	8.0	0.38	0.98
28	1.9	7.6	0.99	0.62
29	9.8	10.7	0.58	0.61
30		3.3	0.83	0.69
31*				
32			0.95	1.50
33	0.4	2.4	0.94	1.04
34	2.9	11.9	0.65	1.90
35		8.4		
Average values.....	2.4	6.0	0.74	1.34

* Postoperative studies not carried out; double amputation performed.

temperature, gives a value which indicates that for every degree of rise in systemic temperature there is an increase in surface temperature due to the shifting of additional blood to the surface, a vasomotor effect. After due consideration of the clinical aspects of the cases, the authors have advised operation arbitrarily in subjects who have had a vasomotor index of 4 or more. The ultimate validity of this

criterion as a measure for the selection of cases for operation can be determined only by carrying out the operation on a large number of patients. A comparison of the temperature curves from protein fever and those following operation shows fairly close approximation.

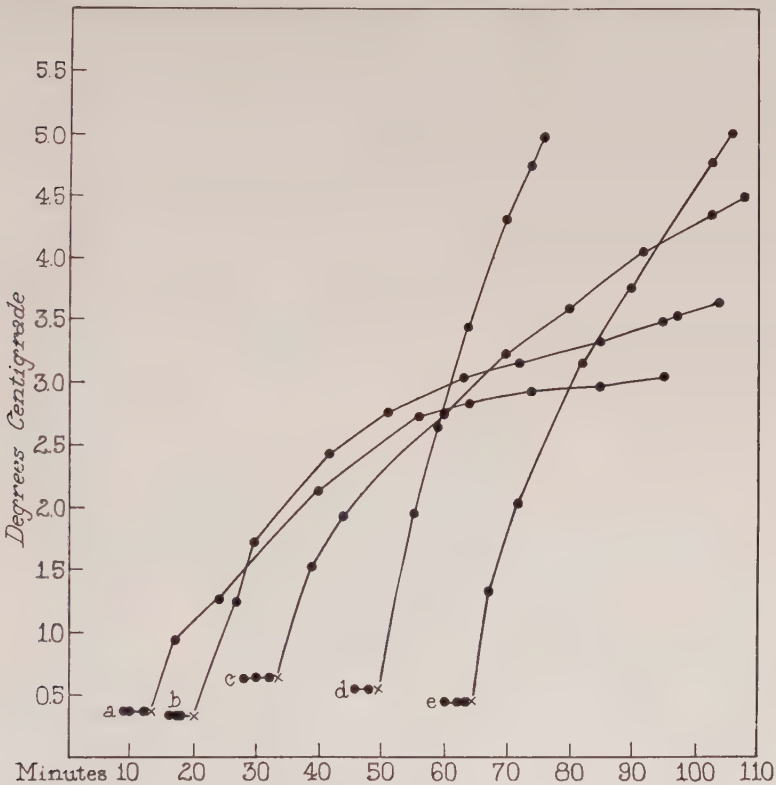

FIG. 173. Graphic representation of the huge increase in the rate of elimination of heat in the feet following lumbar ganglionectomy. *a*, before operation, 0.69 calorie; *b*, before operation, 1.10 calories; *c*, twelve weeks after operation, 1.68 calories; *d*, six months after operation, 5.20 calories; *e*, six months after operation, 3.15 calories.

Fifteen patients with thrombo-angiitis obliterans affecting the lower extremities, have undergone lumbar ganglionectomy. The increases in the surface temperature following this operation are quite different from those occurring in subjects with non-occluded vessels. The increases are less; they lack uniformity in the different digits, con-

trary to that seen in cases of Raynaud's disease and in other conditions in which there are patent vessels. Huge increases in the rate of heat-elimination are noted in some cases (Fig. 173). The healing of ulcers, relief from pain and marked improvement have been observed in

TABLE XIV

SUBACUTE ARTHRITIS INVOLVING THE FEET. SURFACE TEMPERATURES BEFORE AND AFTER LUMBAR GANGLIONECTOMY*

DATE	TEMPERATURE		RIGHT				LEFT				COMMENT
	Mouth	Room	Thigh	Leg	Foot	Toes	Thigh	Leg	Foot	Toes	
1926	°C.	°C.									
May 19	36.6	24.0					34.8	34.0	35.0	25.6	
" 19	36.7	24.1					35.0	34.0	34.3	27.8	
" 20	37.0	23.0						33.0	33.9	26.0	
June 1	37.2		34.7	34.5	35.7	36.1	35.1	35.6	35.9	36.3	Lumbar ganglionectomy
" 2	37.4		36.5	36.1	35.8	36.4					
" 3	37.7						36.1	35.3	35.9	35.5	Feet warm and dry
" 5	37.7		33.6	33.5	34.3	34.7	34.0	33.3	34.5	34.8	
" 7	36.6		35.2	34.6	34.0	34.5	34.8	34.5	34.8	34.8	
" 9	37.2		36.5	35.1	35.8	33.4	35.7	34.3	36.0	33.6	
" 10	37.2		35.7	34.3	36.0	33.6	36.5	35.1	35.8	33.4	
" 11	37.2		35.6	34.7	35.3	33.8	36.3	34.9	35.3	33.7	
" 14	36.8		33.7	33.7	34.7	33.3	34.7	34.4	35.5	34.0	
" 19	36.7	26.2					35.5	34.6	36.3	35.5	
Aug. 4	37.0	28.0					35.7	35.7	36.0	36.0	Feet warm; no pain
" 9	37.0	22.7						35.5	35.0	36.0	Swelling disappeared
1928											
Nov. 16	37.0	23.5	33.6	33.3	33.0	32.6	33.9	33.2	33.6	32.9	Weather cold
" 18	36.6	22.5	34.8	33.1	33.1	34.5	34.3	33.8	33.9	34.0	Feet warm and dry; no pain or arthritis in feet

* Case 13, woman aged thirty-four years.

many cases. The relief from pain following sympathetic ganglionectomy is frequently striking and is not entirely explained by the increased vasodilatation. After the febrile reaction that follows the administration of foreign protein in some cases, relief from the so-called "rest pain" or ulcer pain may persist for several days, long after

the phase of dilatation has passed. Probably diminution of anoxemia in the tissues and riddance of irritating metabolites are important factors in producing the effect. Fifteen patients have been operated upon, of whom three have undergone subsequent amputation of one leg; in two cases, with gross gangrene of the feet at the time of operation, bilateral amputation was subsequently necessary. The duration of the vasodilatation obtained by operation in these cases is subject to the behavior of the primary disease. Progression of thrombosis in the arteries may occur regardless of operative measures, and large segments of arteries supplying collateral circulation may become thrombosed. In one case, one year after operation, there was thrombosis of both femoral arteries, probably extending into the iliac arteries and there occurred a sharp and sudden diminution of the blood-supply to the feet.

In another instance a woman aged thirty-four years, with subacute arthritis, underwent lumbar ganglionectomy, June 1, 1926. This case was reported in detail by Rowntree and Adson (1, 52, 53) who discussed the rationale of this treatment. The pre-operative surface temperature of the feet was fairly low; moderate acrocyanosis was present. Complete studies of the temperature are shown in Table XIV. Diminution in vasodilatation was not found thirty months later. The clinical improvement was startling and was maintained.

Studies on the Vessels of Amputated Limbs in Cases in Which Lumbar Ganglionectomy Had Been Performed

Horton (26) has determined in the amputated leg the effects of lumbar ganglionectomy on the capacity of the arterial tree. Several of his experiments are given:

Experiment 1. In a patient with thrombo-angiitis obliterans, lumbar ganglionectomy was performed. Ascending thrombosis of the femoral and iliac arteries then developed; sixty days after the lumbar ganglionectomy, amputation was necessary because of gangrene of the distal half of the foot.

	gm.
Weight of amputated leg	1155
Weight of leg plus mercury injected under pressure of 50 mm. of mercury with complete filling	1500
Content of arterial bed in grams of mercury filling, ratio of 345: 1155, or 30 per cent	345

Experiment 2 (control). The leg was amputated from a patient with thromboangiitis obliterans, without previous ganglionectomy. The level of amputation was comparable to that in Experiment 1.

	gm.
Weight of amputated leg	1940
Weight of leg plus mercury injected under pressure of 50 mm. of mercury with complete filling of the arterial bed	2072
Content of arterial bed in grams of mercury filling, ratio of 132: 1940, or 6.7 per cent	132

FIG. 174. Photograph showing the leg amputated from a patient with thromboangiitis obliterans. The main arteries are closed and the collateral circulation is poor.

Roentgenographic studies made by Horton (26) after the injection of mercury into the arterial bed in amputated legs in cases of thromboangiitis obliterans, bring out in a striking manner further confirmation of the vasodilator effects of ganglionectomy. In the amputated legs of subjects who have had lumbar ganglionectomy, the roentgenographic shadow of the arteries containing mercury is wider and the collaterals are more prominent than in cases in which ganglionectomy has not been done. The mercury passes through the arterioles into the capillary and venous beds, an observation which has never been made in limbs from control subjects (Figs. 174 and 175). Further

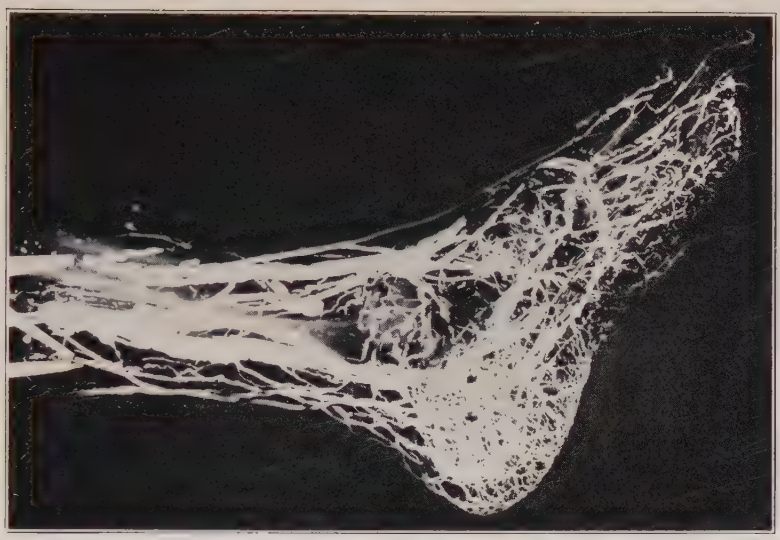

FIG. 175. Photograph showing the leg amputated from a patient with thromboangiitis obliterans, who had undergone lumbar ganglionectomy ten months previously. Collateral vessels show up heavily. There is marked filling of the non-diseased segments of the arteries. Mercury passes into the veins.

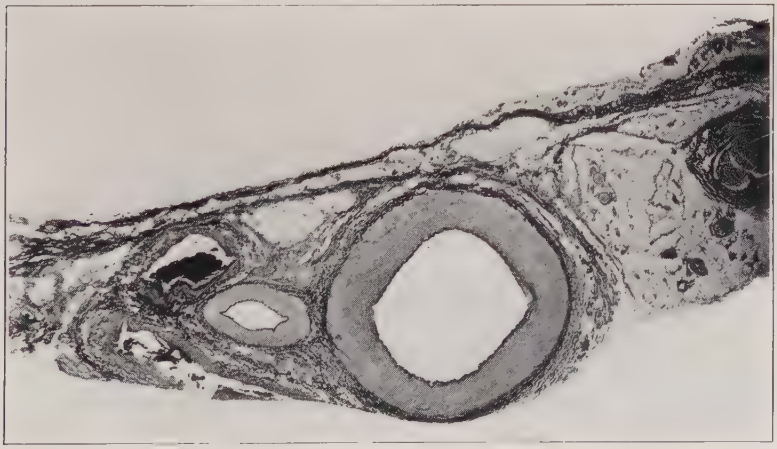

FIG. 176. Photograph showing a cross-section of the dorsalis pedis artery six months after lumbar ganglionectomy.

information was obtained from a pathological study of the vessels in a subject who had undergone a bilateral lumbar ganglionectomy sixteen months previously. Bilateral amputation was done for gangrene of both feet due to progressive, ascending thrombosis involving the iliac arteries (Fig. 176.) Sections were taken through the unoccluded dorsalis pedis artery, and then compared with the dorsalis pedis artery of a control subject. The inference from this examination is that after lumbar ganglionectomy, marked dilatation of the lumen of the arteries apparently exists with atrophy of the medial layer of the arterial wall. The ratio of vessel-lumen to vessel-wall is apparently increased 3.5:1 cm. (The normal ratio in arterioles, according to Anderson, Kernohan and Keith (5), is 2:1.)

The observations of Horton (26) are in line with those of Kerper and Collier (37) who made histological studies on the vessel-changes in the goat and in the cat after unilateral extirpation of the lumbar sympathetic trunk. In the vessels in the limb of the goat, in the distal portions of the denervated vascular tree, atrophy of the muscle-fibers, apparent dilatation of the arterial lumen and endematous swelling in the muscle-cells were noted, similar to the change in the circular muscles found in vessels after reduced functional excitation, of atrophy from disuse. These studies seem to give anatomical proof of the permanent dilative effects of the extirpation of the lumbar ganglion and trunk with an increased flow of blood in the denervated limbs.

Muscle-Tonus: Clinical Observations after Lumbar Sympathetic Ganglionectomy

The influence of the sympathetic nervous system on striated muscle and muscle-tonus had been considered a problem of experimental physiology until Royle (55) and Hunter (29) presented experimental and clinical data seemingly justifying a surgical procedure, "ramisection," which Royle proposed and carried out in spastic diseases.

Foerster (18) advocated section of dorsal roots in selected cases of spasticity, hoping to reduce the hyperactivity of muscles by interrupting the sensory reflexes. Stoeffels' operation (59) of fasciculectomy reduces the innervation to the spastic muscle and thus attempts to bring about a balance of antagonizing muscles.

Neither the Stoeffels nor the Foerster operation offered a satisfactory solution in the treatment of spastic paralysis. Therefore, the present authors proceeded to employ the surgical methods suggested by

Royle, keeping in mind that the anatomy and the physiological function of sympathetic innervated striated muscle are matters of conjecture rather than of established fact. In order to make the lumbar ramisection more effective in interrupting the efferent sympathetic fibers to the lumbosacral nerves they resected the sympathetic trunk, with the second, third and fourth ganglia. A simple section of the sympathetic trunk below the second lumbar ganglion might be sufficient. However, the distribution of the rami from the lumbar ganglia is irregular and not constant. Therefore, since complications have not arisen from the removal of ganglia, it was decided to carry out the resection of the trunks and ganglia in order to make the operation more complete.

The authors' experience, in treating spastic paralysis, has shown that it is possible to reduce spasticity of the lower extremities in patients suffering from cerebral diplegia, but that little is accomplished in cases in which the spacticity is due to unilateral cerebrovascular disturbances. Nothing has been accomplished in the treatment of spasticity resulting from disease or injury of the spinal cord, and operation has been of little or no value in patients suffering from Parkinson's disease. Although operation may reduce the spasticity, it fails to alter the tremor or to interrupt the course of the disease. Therefore, the patient is dissatisfied with the result obtained. Neither has it been possible to alter the ataxia or the athetosis associated with Little's disease. Therefore, the operation is being employed only in a rather selected group of cases suffering from birth injuries, in children, who are old enough to have sufficient mentality to co-operate in the program of re-education. They must be free from athetosis and ataxia; they must be able to stand, although they may be too spastic to walk.

The operation should not be regarded as a cure-all for spasticity, but should be considered as a measure that may be used in conjunction with other measures to improve the status of the patient. Other forms of treatment should be employed first, such as active and passive exercises, tendon stretching, plaster bandages, braces, tendon lengthening with subsequent support and exercises, Stoeffels' operation.

The fact that the Royle operation (56) has not been so effective on the upper as on the lower extremities, would indicate that the operation is incomplete. Royle's more recent operation of section of the trunk

will be more effective, no doubt, in the treatment of conditions of the upper extremities. This can be further improved, the authors believe, by the addition of the dorsal ganglionectomy suggested by them.

EFFECT ON THE VESSELS OF REMOVAL OF THE INFERIOR CERVICAL GANGLION, THE FIRST AND SECOND THORACIC SYMPATHETIC GANGLIA, AND THE INTERVENING TRUNK

This group comprises four cases of Raynaud's disease of the upper extremities, one case of subacute arthritis of the hands, and two cases of scleroderma affecting principally the hands.

TABLE XV

VARIOUS DISEASES INVOLVING ARTERIES; CHANGES IN SURFACE TEMPERATURE* AND RATE OF ELIMINATION OF HEAT IN THE FINGERS, FOLLOWING BILATERAL THORACIC GANGLIONECTOMY

CASE NO.	SKIN-TEMPERATURE, AVERAGE OF SEVERAL READINGS			HEAT-ELIMINATION, IN SMALL CALORIES, EACH MINUTE FOR EACH SQUARE INCH OF SURFACE AREA		DIAGNOSIS
	Before Operation	After Operation	Increase	Before Operation	After Operation	
	°C.	°C.	°C.			
16	21.0	32.7	11.7	10	34	Raynaud's disease
19	23.3	32.8	9.5	22	80	Raynaud's disease
13	23.6	31.2	7.6	82	118	Arthritis of hands
36	24.9	28.0	3.1	70	140	Scleroderma
37	25.6	29.6	4.0	27	80	Scleroderma
38	23.3	30.2	6.9	47	63	Raynaud's disease
39	19.6	30.7	11.1	42	64	Raynaud's disease

* Average readings of all fingers for different days.

Surface temperature in the hands sharply increased after operation in the four cases of Raynaud's disease. The average of many readings of the skin-temperature of the fingers showed increases of as much as 11.7°C., after operation. The average increase for the four cases was 9.8°C. The pre-operative and postoperative observations were carried out at comparable room temperature. The patient with subacute arthritis (Case 13) had fairly cold hands before operation, as is quite common in subjects with this disease. The increase in the skin-

FIG. 177. Photograph showing the appearance of the two hands fifteen days after left thoracic sympathetic ganglionectomy in a case of Raynaud's disease.

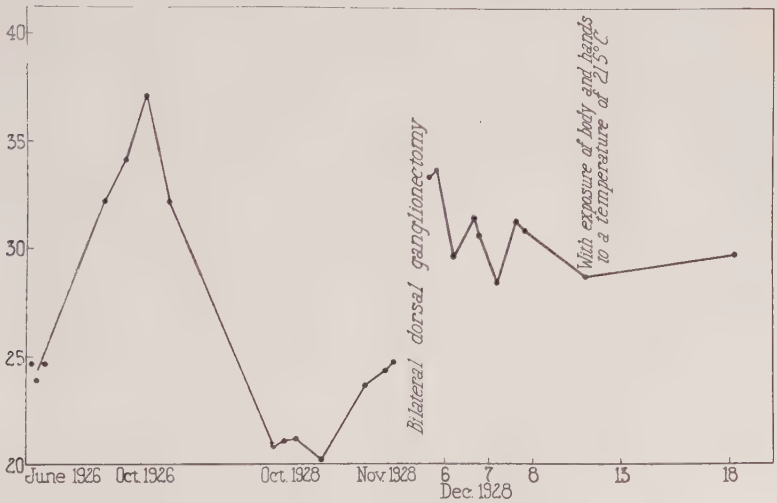

FIG. 178. Graphic representation of vasomotor activity as studied by the surface temperature of the hands before and after dorsal ganglionectomy.

temperature following operation, calculated from the average of many readings, was 7.6°C. on the skin of the digits. In all patients with vascular disease there were comparable increases in the rate of heat-

TABLE XVI

SURFACE TEMPERATURE TWENTY-FOUR DAYS AFTER THE EXCISION OF THE RIGHT FIRST AND SECOND THORACIC GANGLIA IN A CASE OF RAYNAUD'S DISEASE

ANTERIOR SURFACE	LEFT SIDE	RIGHT SIDE
	°C.	°C.
Forehead	33.0	34.0
Cheek	34.2	34.4
Lower jaw	33.9	34.3
Neck	33.6	34.1
Subclavicular area	34.0	32.7
Nipple line	34.0	33.4
Costal margin	34.0	33.7
POSTERIOR SURFACE		
Occiput	32.0	33.1
Lower part of neck	33.1	33.6
Interscapular area	32.9	33.3
Lower scapular area	33.0	33.3

TABLE XVII

SURFACE TEMPERATURE EIGHT AND NINE DAYS AFTER THE REMOVAL OF THE LEFT FIRST AND SECOND THORACIC GANGLIA IN A CASE OF SCLERODERMA

AREA	LEFT SIDE	RIGHT SIDE
	°C.	°C.
Forehead	32.2	31.1
Cheek	31.9	31.3
Neck	31.6	31.9
Anterior part of chest	32.7	32.0

elimination, varying from 70 to 300 per cent. These studies (4) indicate that there was a large increase in the volume-flow of blood,—a fact that was borne out by the clinical improvement (Fig. 177). The thermometric studies were carried out from one to four months after operation; with this interval of time, vasodilatation had not dimin-

ished. In one case of Raynaud's disease daily determination of the skin temperature of the hands, which was noted over a period of years with great variations in outdoor and room temperatures, showed huge changes in the skin-temperature; following operation the residual vasomotor activity and the range in surface temperature of the affected part were much less (Fig. 178).

Vasodilatation of the vessels of the face was carefully studied in two cases, after unilateral removal of the first and second thoracic sympathetic trunk and ganglia, the unaffected side serving as a control. The first patient was examined with thermocouples, the surface temperature of the face and neck being determined at different descending levels, averaging 5 cm. apart.

In a case of Raynaud's disease (Case 19) determinations of surface temperature twenty-four days after excision of the first and second right thoracic ganglia were as shown in Table XVI.

In a case of scleroderma of the hands and face (Case 36) determinations of surface temperature eight and nine days after removal of the left first and second thoracic ganglia were as shown in Table XVII.

Observations on the Surface Capillaries

As was noted previously, vasomotor fibers have not been demonstrated in the capillaries in the skin of human beings. There is, however, considerable collateral evidence to indicate that such fibers may exist. The pallor in the skin induced by psychic effects and the attacks of blanching in the extremities noted in subjects with vasospastic disturbances, are commonplace evidence of neurogenic control of the minute surface vessels. Reflex dilatation of these vessels in certain areas is frequently observed. Besides the probable neurogenic basis concerned with the behavior of the smallest vessels, various metabolites and perhaps hormonal substances are involved. In cases of Raynaud's disease the effect produced by section of the vasomotor nerves on the surface capillaries, is of extreme interest in this connection. Visual information can be obtained by the use of the microscope and by adequate illumination as first employed by Lombard (49). The following observations have been made:

In cases of Raynaud's disease, in which vasoconstrictive phenomena of the acral areas are the basic disturbance, there is loss of capillary tonus when this condition has persisted for a considerable period of time. The hands are continually cyanotic; recovery to the stage of

rubor and resumption of active capillary circulation become increasingly difficult. The appearance of the nailfold capillaries is characteristic (9); there are large dilated loops and dilated venules containing static cyanotic blood due to a low content of oxygen. When a movement of capillary blood occurs, the flow is slow; the blood enters the loops in segments, lending a broken or segmented appearance to the loops. Following resection of thoracic ganglia, the hands become warm, and maintain a fairly normal pink color; the reflex changes in the color of the skin are abolished or are greatly impaired. The

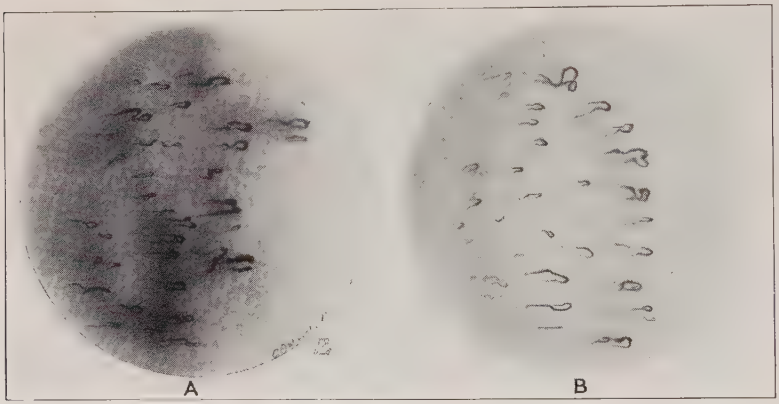

Fig. 179. Photograph showing: *A*, capillaries of the nailfold before operation. Venules and capillaries are dilated. The capillary blood is stationary or very intermittent, giving a cyanotic color to the skin. *B*, capillaries of the nailfold after operation. The capillary loops are narrower. Venous stasis has disappeared. The capillary flow is rapid and uniform, giving the skin a normal pink color.

capillary loops are narrower, the outlines are more clearly defined, and a lesser number are in evidence. The flow is rapid and the blood is red in color. The venules are narrower or become invisible to microscopic inspection (Fig. 179). In subjects without vasomotor disturbances, such as those with spastic paraplegia, observations of the skin on the feet, after lumbar ganglionectomy, did not reveal change in color; and demonstrable variations were not noted in the capillaries.

There has not been evidence in any case of this series, at least with the methods available, to indicate that capillary dilatation follows interruption of the vasomotor nerves. In one case of Raynaud's disease it was noted that after operation complete recovery of capillary

tonus did not follow. The tips of the fingers, although warm, remained red; this was accentuated by the dependent position, and the normal color was obtained by elevation. The capillaries remained dilated but to a lesser degree than before operation. The flow in the loops was rapid and uninterrupted, indicating abeyance of the arteriolar spasm.

Comment. The foregoing observations lend support to the belief that factors other than those of nerve origin are of importance in the maintenance of capillary tonus, that tonus is restored to some degree by blocking the vasoconstrictor fibers, and that probably this restoration is brought about by the production of an uninterrupted flow of arterial blood through the capillary loops. The effect of stasis in the capillary blood, with high concentration of carbon-dioxide or perhaps of other acid metabolites, seems more effective than the neurogenic factor in modifying tonus in the surface capillaries. As tonus of capillaries may not be completely restored after operation it seems likely that permanent loss of tonus occurs when the vasoconstrictive disease has been present for long periods of time.

Interference with Sweating Following Lumbar and Thoracic Ganglionectomy

The anatomical pathways of the sweat-fibers for the posterior extremities in the cat have been worked out with great care by Langley (42). He found that the fibers leave the spinal cord chiefly in the first and second lumbar nerves, enter the sympathetic chain and emerge from this in the postganglionic fibers which pass from the sixth lumbar to the second sacral ganglia. They then join the nerves comprising the sciatic plexus. For the anterior extremities the fibers leave the spinal cord in the thoracic nerves from the fourth to the tenth, enter the sympathetic chain and pass upwards to the first thoracic ganglion where they are continued as postganglionic fibers and communicate with the nerves forming the brachial plexus. It has been shown that the sweat-nerves are genuine secretory nerves and that their action cannot be explained merely as causing a direct variation in the blood-flow.

It was found in every case that after lumbar ganglionectomy, perspiration, as determined by the palpating hand, disappeared in the feet and lower part of the legs to a variable level at or just below the knee. The driest areas occurred in the feet. In one case of spastic

paraplegia desiccation in the soles of the feet was extreme, producing a condition similar to that observed in chronic icthyosis (Fig. 180). Disagreeable or untoward symptoms did not result from the disappearance of sweating except in one case of Raynaud's disease with sclerodermal changes in the skin of the feet; in this case the inhibition of sweating and the dryness of the skin produced small fissures over the malleoli. Complete studies were carried out in three cases to determine the exact levels for the interference with sweating. The studies were made with cobalt-blue test-papers and by means of a

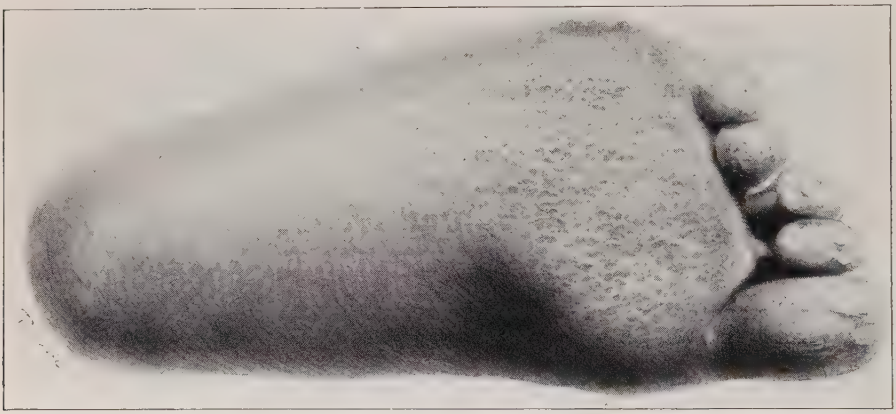

Fig. 180. Photograph showing the appearance of the skin of the palmar surface of the foot, following lumbar ganglionectomy.

miniature galvanic cell applied to the skin; the resultant current which was set up in the presence of electrolytes in solution (sweat) could be read by the swing of the galvanometer. The patients were placed in a heated chamber for forty minutes at a temperature varying from 45° to 46°C., or until such time as visible sweating occurred over the abdomen. In the three cases in which lumbar ganglionectomy had been performed, respectively, one month, eighteen months and thirty-six months previously (Fig. 181), there was considerable variation in the line of demarcation between areas in which there was sweating and areas in which sweating was absent. In Case 16, in

which the operation had been performed three years previously, the upper limit of the area in which sweating was absent, was lower on the right leg than on the left. When compared with the mapping in Case 14 in which operation had been done eighteen months previously, considerable difference was observed. In Case 14 the dry areas extended to Poupart's ligament anteriorly and to the iliac crest posteriorly. There was an area along the mesial surfaces of the thigh in which sweating was present. In this case isolated droplets of sweat could also be detected in the dry skin of the lower extremities. In Case 19, in which operation had been performed one month pre-

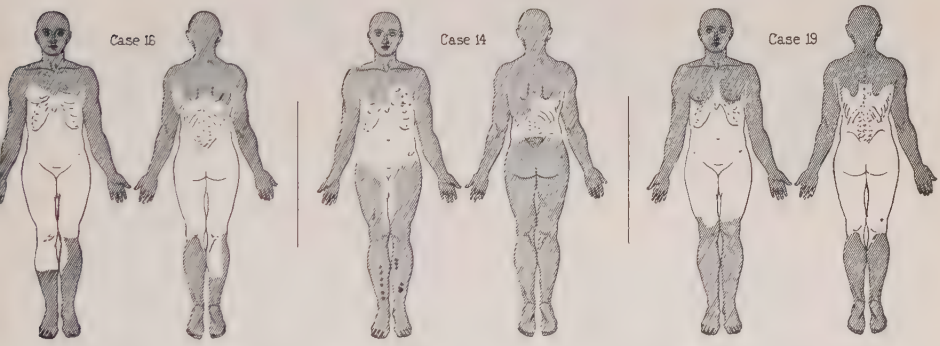

FIG. 181. Diagram showing shaded areas which indicate the absence of sweating under conditions of high environmental temperature. The black dots in Case 14 represent isolated droplets of sweat.

viously, interference with sweating was noted up to a line about 5 cm. above the knees anteriorly and to the level of the popliteal space posteriorly.

The areas in which sweating was absent in the upper extremities in the three subjects were found to be more uniform than were those of the lower extremities. Roughly, the upper areas include the head and neck, extending down to the nipple anteriorly and to the lower border of the scapulas posteriorly. The axillae and mesial surfaces of the upper parts of the arms were moist. The driest areas were on the hands, although excessive scaling, as noted on the feet, was not

observed. The loss of sweating is probably permanent; at least it has persisted in Case 16 up to three years after operation. In patients who have had dorsal and lumbar operations, the total area of the body-surface over which there is sweating, is markedly reduced. This raises the question as to whether the heat-regulating mechanism of the body is not impaired. Some information has been obtained on this point by following the systemic temperature of one of these subjects while in the heating chamber. The systemic temperature reached 99.5°F. when the temperature of the chamber was increased to 45°C., the equivalent of 113°F. Prolonged observations on the effects of summer temperature and active exercise will be necessary to determine this point. It is probable that this reduction in area of the body over which sweating occurs, may produce untoward symptoms under abnormal environmental conditions.

Pilocarpine was given to four subjects after lumbar and dorsal ganglionectomy, and visible sweating was induced in the areas usually dry. This is evidence that degeneration of the sympathetic nerve-endings in the sweat-glands had not occurred within the periods of the postoperative observations.

Pilomotor Reactions

It is generally assumed that the pilomotor fibers follow the same general course as the secretory fibers to the sweat-glands. In the patients observed, it was noticed that there was less of the pilomotor reaction in all those who had undergone lumbar ganglionectomy. The loss persisted in an extreme case up to three years. The zone of demarcation could not be accurately determined by inspection, for the dryness of the skin sometimes seriously interfered with the visualization of the pilomotor reaction. Roughly, in the lower extremities the areas of absent pilomotor reactions were approximately the same as those in which sweating was absent. In the upper extremities, the pilomotor reflex was absent in the arms but was present to a variable degree over the shoulders and back.

STUDIES ON THE ACCELERATOR RESPONSE OF THE HEART AFTER THE EXCISION OF THE INFERIOR CERVICAL AND THE FIRST AND SECOND THORACIC GANGLIA

The accelerator nerves to the heart, as summarized by Howell (27), arise from the spinal cord in the anterior roots of the third, fourth

and fifth spinal nerves; they may emerge also in the first and second thoracic nerves. Variations are found in different animals. These acclerator nerves pass to the first thoracic ganglion as the preganglionic fibers or white rami and then, by way of the annulus of Vieussens, to the inferior cervical ganglion. Some fibers end in synapses in the first thoracic ganglion; and others, in the inferior cervical ganglion. None are found above the inferior cervical ganglion. Several investigators have maintained that acclerator fibers are present in the vagus. It was shown by Hunt (28) that the accelerator fibers to the heart maintain it in a state of tonic activity and that cutting these nerves in animals produces a decrease in the rate of of the heart. The inhibitory fibers in the vagus create a balance between two antagonistic actions. This, no doubt, makes the heart more responsive to reflex adjustments.

Studies on the cardiac response to exercise were carried out on three patients after the excision of the inferior cervical and first and second thoracic ganglia.

Case 19. In a patient with Raynaud's disease, twenty-one days after removal of the right first and second thoracic ganglia, the blood-pressure in millimeters of mercury, with the patient at rest, was 108 to 110 systolic and 70 diastolic; the pulse-rate was, at various times, 81, 86, 84. Sixty seconds after the patient had climbed three flights of stairs, the blood-pressure readings were as follows: systolic 110, diastolic 70; and again, systolic 108, diastolic 72. The pulse-rate at the time of these readings was 89 and 84, respectively. After the patient had hopped on one foot thirty times, the blood-pressure was 110 systolic and 70 diastolic, and the pulse-rate was 84.

Thirty days after right thoracic ganglionectomy, the blood-pressure with the patient at rest was systolic 110 and diastolic 76 to 80; three readings of the cardiac rate, taken at this time, were 90, 93 and 90. The patient was required to hop fifty times on one foot. Blood-pressure readings after thirty seconds were systolic 98 and diastolic 92; after sixty seconds, systolic 98 and diastolic 88; after 120 seconds, systolic 100 and diastolic 82; the corresponding cardiac rates were 102, 98 and 94. Cardiac rates were taken also after 180 seconds and after 240 seconds; these readings were 89 and 81, respectively.

Sixty-six days after right dorsal ganglionectomy, and twenty-four days after the removal of the first and second, and inferior cervical thoracic ganglia on the left side, with the patient at rest, blood-pressure readings were systolic 112 and diastolic 70; and again, systolic 114 and diastolic 72. The cardiac rates taken four times at the same examination read 68, 68, 76 and 76. After the patient had walked up three flights of stairs, the cardiac rates were 132, 124, 108 and 100. At the end of two and a half minutes the rate had dropped to 84.

Forty-one days after the thoracic and cervical operation, with the patient at rest, blood-pressure readings were systolic 106 and diastolic 60; and again, systolic

106 and diastolic 68. Three readings of the cardiac rate at this time were 62, 66 and 70.

After the patient had walked up three flights of stairs, the readings were as follows: at the end of one minute, blood-pressure, systolic 115, diastolic 74, and cardiac rate 110; at the end of two minutes, blood pressure, systolic 108, diastolic 68, and cardiac rate 66. At the end of 8 minutes, the cardiac rate was 70.

The cardiac response in this patient indicates that after the removal of the first and second thoracic ganglia on the right side there was moderate or slight acceleration of the heart following moderate grades of exercise. However, when twenty-four days had elapsed after the operation had been carried out on both right and left sides and when more severe exercise had been taken, rapid acceleration of the cardiac rate was noted although the reaction was subject to variation. Abnormal symptoms or signs did not appear following these exercises.

Case 13. A woman, aged thirty-four years, with subacute arthritis, had undergone resection of a lumbar ganglion eighteen months previously and bilateral resection of the first and second thoracic and inferior cervical ganglia twenty-four days previously. With the patient at rest, blood-pressure readings were systolic 156 and diastolic 100, and the cardiac rate was 64. After the patient had walked up three flights of stairs, readings were as follows: blood-pressure, systolic 170 and diastolic 106, and cardiac rate 104; at the end of one minute, blood-pressure, systolic 174, diastolic 108, and cardiac rate 72; at the end of two minutes, blood-pressure, systolic 166, diastolic 100, and cardiac rate 64; at the end of three minutes, blood-pressure, systolic 160, diastolic 100, and cardiac rate 64; at the end of four minutes, blood-pressure, systolic 160, diastolic 100, and cardiac rate 66; and at the end of five minutes blood-pressure, systolic 156, diastolic 100, and cardiac rate 68. Half an hour after the last observation, 0.6 mg. of atropine was given by mouth; the mouth became dry and the pupils were dilated. With the patient at rest, blood-pressure readings were systolic 150 and diastolic 100, and the cardiac rate was 72. After the patient had walked up three flights of stairs, readings were as follows: blood-pressure, systolic 175, diastolic 112, and cardiac rate 100; at the end of one minute, blood-pressure, systolic 168, diastolic 116, and cardiac rate 70; at the end of two minutes, blood-pressure, systolic 160, diastolic 104, and cardiac rate 76; and at the end of three minutes, blood-pressure, systolic 162, diastolic 104, and cardiac rate 74.

Twenty-seven days after operation, with the patient standing, the pulse-rate was 79 to 80. After the patient had climbed three flights of stairs, the pulse-rate was 106; two minutes later it was 80.

The accelerator effect of exercise was preserved in this patient although the response was less pronounced than in the normal controls. Abnormal subjective symptoms were not complained of, and dyspnea on exertion was of the usual type. Following mild atropinization, acceleration was present in a similar degree.

Case 16. In a woman, aged twenty-five years, with Raynaud's disease thirty months had elapsed after bilateral cervical ganglionectomy, with removal of all or cervical portions of the stellate and middle cervical ganglia through the anterior approach. The operation had been followed by bilateral Horner's syndrome, but without relief to the vasospastic disturbance of the hands. With the patient at rest, blood-pressure readings were systolic 108, diastolic 70, and the cardiac rate

was 84. After the patient had climbed three flights of stairs, readings were as follows: blood-pressure, systolic 135, diastolic 75, and the cardiac rate 148; and at the end of two minutes, blood-pressure, systolic 112, diastolic 74, and the cardiac rate 64.

Thirty-seven days after bilateral removal of the first and second thoracic ganglia, with the patient at rest, the blood-pressure readings were systolic 100, diastolic 60, and the cardiac rate was 70. After the patient had climbed three flights of stairs, readings were as follows: blood-pressure, systolic 118, diastolic 78, and cardiac rate 106; and at the end of one minute, blood-pressure, systolic 100, diastolic 58, and cardiac rate 76. On another day, the cardiac rate was as follows: with the patient at rest, 60; with the patient standing, 60; immediately after rapid walking, 80; and thirty seconds later, 64.

Twenty minutes after 2 mg. of atropine was given by mouth, the mouth was excessively dry, and the cardiac rate was 76. The cardiac rate was then taken after two minutes, three minutes, five minutes, and nine minutes; these readings, respectively, were 80, 92, 98 and 100. After rapid walking, the cardiac rate was 104; half a minute later it was 100; after two minutes it was 92; and after four minutes it was 76.

The data in this case give evidence that the cardiac response to exercise was preserved two and a half years after cervical ganglionectomy in which the inferior and middle cervical ganglia were removed; that after the removal of the first and second dorsal ganglia, the accelerator response to exercise was preserved but perhaps was less effective; and that following the administration of atropine, the acceleration of the heart was pronounced.

This patient complained of palpitation of the heart while at rest, following cervical ganglionectomy. During the ensuing period of two years, the signs and symptoms of irritable heart developed. According to the patient's statement, during periods of palpitation the rate of the heart was somewhat elevated. After the dorsal sympathetic ganglionectomy, palpitation still persisted in a mild degree but with a normal or slowed rate. Electrocardiographic tracings did not reveal significant changes before or after the dorsal ganglionectomy.

Comment. The foregoing studies are of interest from several standpoints. First, the patients were young and were not suspected of having organic disease of the heart; the observations cannot be compared with those made on older subjects with angina pectoris. Second, as has been pointed out (pp. 726–727), complete removal of the cervicodorsal, or what is known as the stellate, ganglion is difficult from the anterior approach. The thoracic portion may be separate from the cervical portion; therefore, it remains problematic after operation by the anterior approach whether extirpation has been complete. By the posterior approach the first and second dorsal ganglia, with the sympathetic trunk, are removed without question. Following this type of operation, the cardiac response seems to show

slight impairment of acceleration in certain subjects; this is not uniform and may be a postoperative exhaustion effect. Evidence was not obtained to indicate that organic changes or serious functional disturbance of the heart are sequelae. Some information on the late effects of cervical ganglionectomy is furnished in Case 16, in which studies three years after operation show fairly normal acceleration of the heart. Further and more complete studies must be carried out. Brüning (11) could not find predominant action of the antagonist to the heart by bilateral removal of the stellate ganglia. Jonnesco and Ionescu (35) have shown that following bilateral extirpation of the stellate ganglia in man the heart retains the ability of accommodation to the usual demands of age. They concluded that the accelerator nerves in man are not vital nerves. Cannon, Lewis, and Britton (14) have demonstrated that with extirpation of the hitherto recognized nerves extending to the cat's heart, acceleration of the heart is still preserved. They presented evidence showing that accessory accelerator fibers from upper thoracic ganglia, below the stellate, mediate the faster beat. The removal of these maintains the cardiac rate within a fairly narrow range. A more recent anatomical study by Ionescu and Enachescu (30) has demonstrated that efferent nerves leave the second to the fifth thoracic ganglia and pass to the heart. This would indicate that cadiac acceleration may be retained after the extirpation of the stellate ganglion, since only a part of the sympathetic nerve-fibers to the heart are removed. (See also Fig. 182, this volume, p. 787; and p. 788.)

In a communication from Dr. Charles W. Greene (23), he stated: "I have experimental animal data that indicate that the heart rate may be influenced both by stimulation, that is, slowing, and by inhibition of the vagus reflexes, that is, acceleration." The information obtained in Case 16, with adequate atropinization, would show that with the effect of the vagus probably completely eliminated, cardiac acceleration still occurs. This further suggests the existence of accessory cardiac efferent nerves.

The following personal communication has been received from Kuntz (41, 42): "We have traced nerves from the thoracic sympathetic trunk into the cardiac plexuses in not less than six cadavers. We find rami of considerable size arising from the third and fourth thoracic sympathetic ganglia. These rami enter the superficial and deep cardiac plexuses. To what extent the fibers of these small rami are distributed to the heart cannot be stated since the pulmonary

plexuses are continuous with the deep cardiac plexus. We are not prepared to say at present whether these nerves are constant in man, although I rather expect that they will be found to be fairly constant."[4]

BERNARD-HORNER'S SYNDROME: OCULOPUPILLARY PHENOMENA AFTER THORACIC GANGLIONECTOMY

Following the extirpation of the inferior cervical or cervicodorsal ganglia or section of the intervening sympathetic innervation of the eye and eyelids, characteristic changes in the pupil and eyelid occur. Dupuy (17), in 1816, noted, after removal of the superior cervical ganglion in horses, vascular injection of the conjunctiva and increased temperature in the ear. Claude Bernard (7), in 1851, was the first to note increased vascularity and elevated surface temperature of the face after resection of the cervical sympathetic cord in rabbits, thus discovering the vasomotor nerves. In 1869, Horner (25) called attention to partial ptosis, contraction of the pupil and elevation of the surface temperature of the face in a patient; he ascribed the condition to a lesion of the sympathetic nerves of the neck on the affected side. Since then, these oculopupillary phenomena have been known as Horner's syndrome. The ocular changes occur immediately after section of the cervical sympathetic cord or resection of the ganglia. The pupil is small, does not react to cocaine or atropine, but retains the reflexes to light and accommodation; there is a narrowing of the palpebral fissure with apparent enophthalmos. The movements of the eyelids are not impaired and the partial ptosis is ascribed to a loss of tonus in the nonstriped muscle-fibers. Various gradations in the intensity of this interesting syndrome are observed. Associated with the ocular phenomena is increased surface temperature of the face on the side on which operation has been performed. Jaboulay and Jonnesco (32) also noted dilatation of the retinal vessels. Leriche and Fontaine (47) have clearly defined the severity and completeness of the oculopupillary syndrome following resection of the cervical sympathetic cord at different levels. They concluded that the sympathetic fibers to the eye leave the sympathetic cord just above the first thoracic ganglion and follow the vessels entering the cranium. Section of the sympa-

[4] This work was reported by Kuntz, A., Kerper, A. H., and Morehouse, A., at the meeting of the American Association of Anatomists, Rochester, New York, March 28 to 30, 1929 (43, 44).

thetic cord at the level of the superior cervical ganglion produces less intense changes than section at the level of the stellate ganglion.

In seven cases, after extirpation of the upper thoracic ganglia, Horner's syndrome was evident immediately after operation. The persistence and completeness of the reaction varied considerably in each case. In Case 19, one of Raynaud's diease, the syndrome was fairly well marked after resection of the right first and second thoracic ganglia. One month after operation, the right pupil was smaller than the pupil on the left side, that on which operation had not been performed. The arteries and veins of the right retina were larger than those on the left. Following cocainization, both pupils became dilated and were of equal size. Fifteen days after removal of the left lower cervical and first and second thoracic ganglia, the left pupil was smaller than the right and dilatation was not induced with cocaine; whereas in the right eye, dilatation occurred. The left palpebral fissure was narrower than the right. These observations indicate that the phenomenon had disappeared from the right eye but was present in complete form in the left eye. Fifty-seven days after the second operation, that on the left side, dilatation was obtained in both eyes following cocainization. At this time, Horner's syndrome was no longer complete in the left eye and was entirely absent in the right eye. In Case 16, one of Raynaud's disease, in which bilateral excision of the lower and middle cervical ganglia was performed on June 10, 1926, the operation was followed by bilateral partial ptosis and contracted pupils; these effects have persisted. Examination, November 8, 1928, showed that both pupils were contracted and equal and that change was not effected by cocainization. Moderate and equal degrees of ptosis had persisted in both eyes. In Case 13, the patient underwent bilateral removal of the lower cervical and first and second thoracic ganglia on November 23, 1928. Eighteen days later both pupils were contracted. Dilatation was not obtained with cocainization. Complete Horner's syndrome was present. In Case 36, that of a young man with scleroderma involving both hands and fore-arms, the left inferior cervical and first and second thoracic ganglia were resected December 11, 1928. Immediately after operation, the left pupil was contracted. A noticeable degree of ptosis was present. On the following day, the small vessels in the sclerotics and conjunctiva were dilated to a degree that simulated mild conjunctivitis. With cocainization, the left pupil was somewhat

dilated, indicating an incomplete Horner's syndrome. The vessels in the left retina were definitely dilated as compared with those on the side on which operation was not performed. Following resection of the right first and second thoracic ganglia, there was a transitory Horner's syndrome of the right eye which practically disappeared in ten days.

Comment. The observations on the ocular changes following cervical and dorsal ganglionectomy indicate that: (*a*) incomplete or temporary Horner's syndrome occurs after resection of the first and second thoracic ganglia; variations are noted on the right and left sides with the same operative procedure; (*b*) a more complete Horner's syndrome occurs after the operation if the inferior cervical portion of the cervicodorsal ganglion is also removed; a similar result was noted following resection of the middle and lower cervical ganglia and the effect in this case has persisted for a period of thirty months; (*c*) dilatation of the arteries and veins occurs constantly after both cervical and dorsal ganglionectomy; (*d*) dilatation of the vessels of the sclerotics and conjunctiva occurred in one patient, in the eye on the side on which operation was performed, and disappeared within five days; and (*e*) increased surface temperature of the face on the affected side occurs with the ocular phenomena.

CUTANEOUS HYPERESTHESIA

Diez noted in his cases that after resection of the cervical sympathetic cord, cutaneous hyperesthesia of the skin appeared on the neck and usually disappeared in a month. After resection of the lumbosacral sympathetic chain, tenderness of the sciatic nerve was constant. In the thirty-six cases in the authors' group in which the lumbar ganglia were removed, there were only two in which sciatic tenderness was present, and this only to a mild degree, passing off within about ten days after operation. Hyperesthesia was not complained of, or elicited on general examination, in any case.

Following thoracic ganglionectomy, cutaneous hyperesthesia was noted in some degree in every case. In two cases this was fairly intense and pain could be elicited after mild stroking of the skin of the arms. The hyperesthetic zone included the arms, neck, and anterior and posterior surfaces of the chest to a level about 7.5 cm. below the clavicles. The area in the region of the wound exhibited the most marked hyperesthesia. Pain in the back, in the region of the wound,

with disclosure on neurological examination of irregular areas of anesthesia, was constant. Soreness of the muscles, nerve-trunks, and large arteries of the arm was brough out by mild palpation. Neurological changes, other than those mentioned accompanying this symptom, were not present. The onset and duration of the hyperesthesia were variable, usually diminishing in from ten days to two weeks and completely disappearing at the end of four or five weeks. The individual sensitivity of the patient was undoubtedly a factor in the subjective severity of this complaint. It seems quite probable that the trauma of the first and second thoracic nerves during operation was the major factor in the causation of the pain. In the last three patients operated upon, greater care was used in preventing trauma to these nerves; in these the pain and hyperesthesia were minimal.

ATROPHY OF THE MUSCLES

Diez (16) has likewise called attention to atrophy of the pectoral, deltoid, trapezius, supraspinous and infraspinous muscles following resection of the middle, inferior cervical and first thoracic ganglia and the trunk. Atrophy became recognizable in from one to three months. Atrophy of the muscles was not noted after lumbosacral ganglionectomy.

The present authors have not observed atrophy of the muscles following lumbar ganglionectomy, at least not during the period of postoperative observation. In one case of Raynaud's disease, studied for a period of three years after lumbar operation, atrophy of the muscles of the leg was not present. Following thoracic ganglionectomy, atrophy of the muscles of the shoulder was noted. There was considerable difference in the degree of atrophy present and in only one case was it striking, namely, in a case of scleroderma in which the trapezius muscle showed well-defined atrophy four weeks after resection of the dorsal ganglia.

SUMMARY

Physiological studies carried out in thirty-six cases before and after lumbar ganglionectomy, demonstrated certain changes after operation. Marked vasodilatation of the arteries of the feet and lower part of the legs, as measured by thermometric methods, has persisted for periods as long as three years. Abolition of reflex sweat-

ing of the feet and lower part of the legs, approximately to the level of the knees, is a constant observation. The loss of the pilomotor reaction occurs in approximately the same areas as does reflex sweating.

Following excision of the first and second thoracic ganglia the following conditions have been observed: marked vasodilatation of the arteries of the hands, and mild vasodilatation of the arteries of the face, neck and upper part of the trunk, as measured by increases in the surface temperature. The loss of reflex sweating and of the pilomotor reaction were in, roughly, the same region. The reaction of cardiac acceleration was preserved but possibly was diminished in degree. Horner's syndrome of variable intensity and persistence was a constant observation. The period of observation after dorsal ganglionectomy has varied from one to six months, and vasodilatation has not diminished in that time.

These physiological changes, indicative of a profound and apparently lasting effect on the vasomotor nerves, with vasodilatation, furnish adequate proof of the efficacy of these operative measures in the treatment of certain forms of peripheral vascular disease.

DISCUSSION

The following questions submitted to Dr. Brown and Dr. Adson before the Commission, together with the answers to them, are here reported verbatim.

Dr. Kuntz: Our attention has been called by various workers on experimental animals to the fact that after sympathectomy circulation returns to approximately normal in the course of about ten days or two weeks. The results shown us here seem to be fairly permanent. What I should like to ask Dr. Brown, is this: Do those vessels dilate only to their normal capacity, that is, the extent to which they have been constricted, so that they remain then at what was their normal caliber, or how are we to explain that difference between these results in the human subject and the results reported in animals under experiment?

Dr. Brown: The arteries and arterioles dilate to a larger size than normal. This has been substantiated by Dr. Horton's work (26). He has demonstrated pathologically that these vessels remain permanently larger in caliber following ganglionectomy and truck-section.

Dr. Kuntz: I should like to ask, what is the effect on the erector pili muscles?

Dr. Brown: The erector pili muscles are paralyzed.

Dr. Kuntz: With regard to Dr. Adson's work, I should like to ask: Would it be feasible, in using the dorsal approach, intentionally to leave intact the white rami to the first thoracic nerve? By removing the trunk below the first white ramus, perhaps all the preganglionic fibers are cut that have to do with the innervation of the upper extremities. By leaving the first white ramus intact, we might avoid some of the effects in the face, that is, the ocular changes, and so forth.

I just wonder if that would be feasible.

Dr. Adson: It is possible to divide the thoracic trunk wherever one chooses but I doubt if it would be feasible. Perhaps we have been rather overanxious to make sure that we have completely interrupted all of the vasoconstrictor fibers to the vessels of the arm and hand.

Dr. Frazier: May I ask Dr. Adson why Horner's syndrome was only transitory in certain instances?

Dr. Adson: I believe that it is due to the fact that the lower cervical ganglion was incompletely removed and that in all probability it receives gray rami from one of the thoracic nerves.

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CHAPTER XXXIV

Part One

SYMPATHECTOMY IN ANGINA PECTORIS

HARRY HYLAND KERR, M.D., C.M., F.A.C.S.

INTRODUCTION

THE extensive literature of the past few years, as well as the personal experience of the author, proves that surgery is beneficial in angina pectoris.[1] The underlying pathology may not be affected by operation, but patients who are totally disabled by the disease may be restored to subnormal activity. As to the prolongation of life by operation, it is too early to draw conclusions.

Admitting that surgery is to be considered as a therapeutic measure, the questions now confronting physicians are the selection of cases and the method of attack. As to the cases suitable for surgery, that problem must remain in the hands of the internist. He is the one best able to make a diagnosis of angina pectoris and to evaluate the dangers from associated coronary, cardiac or other pathology. Most authorities agree that cases of coronary thrombosis should be rigidly excluded from surgical interference. One of the author's cases with a clear history of coronary thrombosis six months before operation was entirely and completely relieved of all attacks of angina pectoris after superior cervical sympathectomy. In another case, coronary thrombosis occurred one month after operation. (This case will be referred to later, pp. 769, 776.)

The selection of the method of attack must depend upon the amount of relief obtained in proportion to the risk involved. The theory of the relief from spasm by the severance of a reflex arc between the

[1] A description of the surgical technique and a review of the literature are included in the author's earlier papers on this subject (30, 31). Recent investigations of importance have also been reported by Bouquet (1), Christopher (2), Coleman and Lyerly (7), Cutler (8, 9), Cutler and Fine (10), Fontaine (14), Fedoroff and Saposchkoff (15), Gonzalo (16), Gernez (17), Goldschneider (18), Hesse (21), Isakowitz (22), Leriche (32), Levine (33), Lilienthal (34, 35), McCulloch (36), Moharrem (37), Pardee (41), Sicard (45), Valerio (48).

cardiac plexus and the central nervous system, seems to be generally accepted. The nerve-supply to the heart is elaborate and variable. Anatomical studies inspired by this problem of surgery in angina pectoris reveal a multitude of connections between the vagus nerve and its branches and the cervical sympathetic chain. The anterior cardiac plexus which inervates the first part of the aorta and anterior coronary artery, is made up principally from the left superior cardiac nerve and the vagus.

It is impossible to demonstrate on the human being the exact physiology of the afferent and the efferent pathways between the heart and the central nervous system. It is supposed that for the most part afferent impulses pass through the middle and the inferior cardiac nerves of the sympathetic system and the vagus to the central nervous system. The efferent impulses in general pass by the left superior cardiac nerve, —a branch of the left superior cervical sympathetic ganglion. By whatever pathways the impulses pass to or from the heart their interruption should break the arc and prevent the spasm of the aorta or coronary arteries, or both. Characteristic pain accompanying the phenomenon is likewise relieved completely or in part by the surgical division of some of the nerves innervating the heart.

A portion of the vagus nerve, the so-called depressor nerve, may be divided or the entire sympathetic supply to the heart may be avulsed. Both methods are reported to have given good clinical results. From a practical standpoint, there are distinct objections to both of these procedures. In man there is no depressor nerve *per se*, so that all the branches of the vagus entering the thorax must be divided to accomplish the desired result. The ramifications of the numerous nerve-anastomoses make this a difficult and uncertain operation. On the other hand, the removal of the entire sympathetic chain extending into the thorax is likewise difficult and frought with danger.

In 1921 Coffey and Brown (4), in attempting the removal of the entire sympathetic chain in two stages, avulsed the superior cervical ganglion at the proposed first sitting. They were surprised to find that this simple procedure gave complete relief from the severe and frequent attacks of angina pectoris. Encouraged by this result many cases have been similarly treated. The effects have justified the early hope that a safe and simple operation would be as satisfactory as the more elaborate procedure. By this means only one pathway to the heart is divided and the danger of partially denervating the heart,

as emphasized by Danielopolu (11, 12), Danielopolu and Hristide (13), is avoided.

A clinical study of twenty cases of angina pectoris treated surgically is reviewed in the present chapter. The first case of this series was operated upon early in 1924; the last, in the latter part of 1928, nearly five years later. Seventeen cases were subjected to superior cervical sympathectomy. In one case the left ganglion nodosum of the vagus was removed by mistake. In one, the complete cervical chain, including the stellate ganglion, was removed on the left side; and, in addition, the superior ganglion on the right. In one instance, the left superior cervical ganglion was removed, and one week later the left stellate and second thoracic ganglia were removed from behind. Of the seventeen superior sympathectomies, five had both the right and left ganglia removed because of a bilateral distribution of pain. A total of twenty-eight operations were performed on twenty patients.

A summary of the physical condition of the twenty cases reveals the following data:

The average age was fifty-six. Nine of the patients were in the fifth decade of life. The youngest case was forty-three and the oldest, seventy.

In every case the blood-Wassermann was negative.

In eleven of the twenty cases, the cardiac examination was negative. In six cases there was cardiac enlargement with murmurs. In two cases the X-ray showed some widening of the aortic arch. In one case there was accentuation of the aortic second sound, with an aortic systolic murmur, produced on exertion.

The blood-pressure was between 120 and 150 in ten cases. In eight it was between 150 and 220. In two it was between 110 and 120.

One patient, aged sixty-two, had had diabetes for nine years. The glycosuria was readily controlled by diet. Insulin had never been given.

The immediate mortality from operation was 5 per cent. One case with coronary thrombosis died twenty minutes after reaching his bed, following a unilateral left superior cervical sympathectomy.

Of the remaining nineteen, seven have subsequently died. One case died eighteen days after the operation, having been free from pain until just before death. The cause of death in this instance may have been coronary thrombosis. One case succumbed to cardiac decompensation three months after operation, having experienced

little, if any, relief from the cardiac pain. One case died nine months after operation of acute cardiac dilatation. He was the youngest on the list (forty-three years of age). He had obtained complete relief from all pain and utterly disregarded the advice of his attending physician to be careful on account of the myocarditis. One case dropped dead while suffering from acute headache, one year and eight months after operation. Though he had had frequent mild attacks of anginal pain since the operation he complained of no pain in the chest before death. Autopsy was not allowed. One case died of myocarditis one year and nine months after operation. She had had nearly complete relief and had enjoyed a subnormal activity. One case died of myocardial insufficiency two years and two months after operation. In this case partial relief from pain had been obtained. The seventh case died of congestive heart-failure, four years after operation. He had been completely relieved by the anginal operation.

The subsequent history of the twelve remaining cases has been followed either through personal visits or recent correspondence. Three of these cases have had complete relief after superior cervical sympathectomies; one case after nearly five years; the other two for four years and nine months, and for three years and nine months, respectively.

In the nine other cases the relief has been nearly complete. As a rule they experience a sense of discomfort beneath the sternum upon unusual exertion. This is promptly relieved by nitroglycerine. Six have returned to their former occupations; one has suffered an apoplectic stroke; and one has developed diabetes. The case in which the vagus ganglion was removed, had an attack of severe substernal pain lasting nearly twelve hours and accompanied by slight fever and leucocytosis about one month after operation. The attending cardiologist considered this an attack of coronary thrombosis. In the two years and nine months following the recovery from this attack he has been free from any severe pain. He cannot walk rapidly up hill without producing substernal discomfort, but he is able to resume his former occupation at a slower gait. His hoarseness, from the vocal-cord paralysis, has entirely recovered. (See also Seelig (43, 44).)

The last case operated upon is too recent to permit of final judgment. A left superior cervical sympathectomy has given only partial relief. One week later the left stellate ganglion and the second thoracic ganglion were removed from behind, by the operation described by Henry of Dublin (19, 20). The relief following the second operation

has been much greater, though the patient occasionally finds it necessary to take nitroglycerine. The results in this instance would lend support to the views of those authors who consider superior ganglionectomy an inadequate procedure.

The experience with this small group of cases has convinced the author that the simple operation of superior ganglionectomy under local anesthesia gives as adequate relief as the more elaborate procedures. The final decision must depend upon a wider, comparative study of case reports.

REPORT OF CASES[2]

Case 1. A. M. W., a woman fifty-seven years old. The patient was first seen on January 31, 1924. She was rather short and stout, weighing 140 pounds. Her blood-pressure was 200 systolic, 90 diastolic. The examination of the blood was normal; the Wassermann, negative; the urine, negative, except for a very faint trace of albumen. The renal function test and the blood-chemistry were within the normal limits. The examination of the heart was negative, showing no enlargement and no cardiac murmurs. The X-ray of the chest was negative.

The present illness began twenty months before admission, with a characteristic attack of angina pectoris. While walking up a slight incline, the patient was seized with a knife-like pain behind the sternum, running down both arms. This experience was repeated innumerable times since then, growing worse until she was finally confined to her room. The slightest exertion, or the ingestion of anything but a small amount of liquid nourishment, produced an attack. The pain responded promptly to the administration of nitroglycerine.

On February 7, 1924, under general anesthesia, the left superior cervical sympathetic ganglion was removed. Following this procedure the patient was free from pain for two days. It recurred, however, on the third day, after the midday meal. On the fourth day she had another typical attack which was immediately relieved by nitroglycerine.

Since the pain was bilateral, on February 14, the right superior cervical sympathetic ganglion was extirpated. The patient was discharged from the hospital on February 23, 1924, without having had a recurrence of the pain. Shortly thereafter while walking, she had a pain which she described as similar to the old pain. It was, however, not nearly so severe and was not referred down the arms. The subsequent history showed occasional attacks of a retrosternal ache which were never referred down the arms. She has had no pain whatever for two months, and has been able to go out and about, and to lead her normal life.

Case 2. W. E. P., a man fifty-four years old. The patient was first seen on February 26, 1924. He gave a typical history of angina pectoris of a few months' duration. The pain was referred only to the right arm and was precipitated by the slightest exertion or by the ingestion of food. His father had died of heart-trouble.

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[2] Cases 1 to 8 of this series were originally published in an earlier report (30). For the histological study of Cases 1 to 20, see pp. 780–782.

The patient had had typhoid fever at the age of twelve years. The venereal history was negative. He used to be a heavy drinker, but had been a total abstainer for seventeen years. During the past ten years his weight had markedly increased and he had dyspnea upon exertion. There had never been any edema of the legs or feet.

The physical examination showed a large man, weighing about 200 pounds. The complexion was pasty and the mucous membranes were pale. The heart was found to be distinctly enlarged; a loud systolic murmur was heard over the entire cardiac area and into the left axilla. The blood-pressure was 200. The physical examination was otherwise essentially negative.

On March 3, 1924, the left superior cervical sympathetic ganglion was extirpated under local anesthesia. The recovery was prompt and satisfactory. The patient never had any return of the anginal pain; and a note of March 22, 1924, stated that he had walked a mile without discomfort. This was nineteen days after the operation. He died four years later without having had any recurrence of the pain.

Case 3. R. H., a man sixty years old. The patient was first seen on March 17, 1924. The present illness began on January 1, 1924, with a typical sharp attack of angina pectoris. Intense pain behind the sternum was referred down the left arm, with a feeling of suffocation and of impending death. These attacks recurred and became more severe so that the patient was either in bed or confined to his room.

The man was rather robust and of the florid type. The blood-pressure was 140 and there was no evidence of arteriosclerosis. The physical examination was essentially negative. The X-ray of the chest showed no abnormalities of the heart or great vessels. The heart sounds were clear.

On March 20, an operation was performed under general anesthesia,—a typical block-incision with extirpation of the superior cervical sympathetic ganglion and its branches. The operative recovery was good. On the third day there was a sharp pain in the lower right quadrant of the abdomen. The leucocyte count was 13,000. The temperature rose gradually during the next few days, and the leucocytes mounted to 20,000. By this time a patch of localized dullness and suspicious râles confirmed the diagnosis of pneumonia. This, however, cleared up promptly, and the patient went to Atlantic City. There was no return of the angina in any form after the operation.

In May, 1924, six weeks after the operation, the patient had an attack of apoplexy of the left side which left him hemiplegic and completely aphasic. The recovery has not been satisfactory; though the patient has been able to be up and around, he has never been able to speak since the stroke. He has never had an attack of angina since the operation.

Case 4. E. B. P., a man fifty-five years old. The patient was first seen on October 22, 1924. He gave a history of recurring attacks of retrosternal pain referred down both arms, for the past two years. He was never vigorous, and had had a severe attack of appendicitis with prolonged postoperative drainage five years previously. Since that time his health had been decidedly impaired. When the attacks of pain began, it was said that the heart showed no abnormalities upon physical examination. Since then, however, he gradually progressed to a state of cardiac decompensation. He was unable to lie down and spent most of

the time standing by his bedside. There was edema of both lower extremities, involving the scrotum and both fore-arms and hands. The pulse-rate was about 95. The heart was markedly enlarged; there was a systolic murmur heard over the precordium and left axilla. The aortic sound was not clear. The blood-pressure was 150. The patient took nitroglycerine repeatedly. When he felt an attack coming on, he would put a hypodermic tablet under his tongue and was usually able to remove it within a few seconds, with the attack averted. He was thoroughly "digitalized" on two separate occasions, without obtaining any relief from the anginal pain or cardiac condition.

On October 18, 1924, left superior cervical sympathectomy was performed under local anesthesia. There was some modification of the pain, though it continued in a lesser degree, still necessitating the use of nitroglycerine. As the pain was bilateral in distribution, a right superior sympathectomy was performed under local anesthesia on October 25th. Again, the condition was not markedly changed and the pain continued both behind the sternum and down both arms.

On November 19, one month after the first operation, the patient was operated upon for the third time, under local anesthesia. The middle and stellate cervical ganglia of the left side were extirpated. This operation was extremely difficult because the patient was apprehensive during the procedure and took nitroglycerine several times. The procedure was carried out, however, without pain from the operative trauma. Following the operation the patient's condition remained essentially unchanged. The retrosternal pain continued and was referred to both arms as before. It was, however, decidedly less severe than before the interference. The cardiac condition grew gradually worse. The patient was never able to lie down; the dyspnea and edema progressed; and he succumbed in January, 1925, three months after the first operation.

In this case, the operation was considered a failure. The angina was not controlled, though it was somewhat modified. The patient died from cardiac decompensation.

Case 5. C. H. F., a man sixty-one years old. The patient was first seen on March 7, 1925. The past history was negative, except for a nervous breakdown about thirty years previously.

For the past three years the patient had complained of soreness, distress and, at times, of actual pain with a feeling of constriction in the upper chest and under the sternum. The pain was frequently transmitted down the arms, particularly the left. The attacks of pain had been increasing during the past few months. At the time of examination it was induced by any exercise, eating or emotion. The patient was always relieved by nitroglycerine (0.005 gr.), placed under the tongue.

The heart examination eighteen months previously showed the size to be normal and the aortic arch not enlarged. The first tone at the apex was of good muscular quality; the second pulmonic tone was normal; the second aortic tone was somewhat accentuated and slightly ringing in quality. A fairly loud, rather harsh systolic murmur was heard at the second right intercostal space. This was faint in the right supraclavicular region and at the midsternum. These aortic sounds were accentuated and the second aortic tone and murmur were increased when the patient was lying down after exercise. The cardiac response to moderate exercise was good.

The examination at the time of observation showed the same conditions, except that the accentuated aortic tone and the aortic systolic murmur were not illicited when the patient was examined at rest and they were very slight after exercise. The physical findings in relation to the aorta were less marked, whereas the subjective symptom, pain, had become worse. The blood-pressure had remained fairly constant over the entire time, averaging about 140 systolic, 80 diastolic. The X-ray of the chest was negative.

On March 11, 1924, under local anesthesia, the left superior cervical sympathetic ganglion was extirpated. Convalescence was smooth and satisfactory. Though the patient had no severe attack of pain after the operation, he complained of some substernal ache, which gradually diminished. At first he continued taking nitroglycerine(0.002 gr.), but as his distress gradually lessened, he practically discontinued the medicine.

The pain entirely disappeared two months after the operation, and did not recur, although the patient resumed his former occupation.

Case 6. T. E. M., a man fifty-two years old. The patient was first seen on March 13, 1925. The illness had begun in December, 1924, with an attack of pain in the chest, radiating to the left arm. It passed off without assistance or medication. In January, 1925, the patient was awakened from a sound sleep at five o'clock one morning, with a typical attack of angina. During this attack, the pulse was very fast and slightly irregular. He never had another frank attack, because, as soon as he felt one coming on, he took nitroglycerine and lay down.

On March 16, 1925, a typical left superior cervical sympathectomy was performed under local anesthesia. Convalescence was satisfactory, and up to the fourth day there was no return of the pain.

A letter dated April 20, 1925, a little over a month after the operation, stated: "I have had some pain in my chest. I suppose I have taken nitroglycerine about four times, which relieved me. I have taken some light exercise in my room with no discomfort. I feel better than I have done for six months prior to operation."

Case 7. G. D., a very stout woman fifty-seven years old. The patient was first seen on April 9, 1925. Seven years previously she had had her first attack of severe subpectoral pain. Since then she had attacks more or less frequently. For the six months prior to observation she was confined to her room and after each attack she was compelled to stay in bed for several days. She stated that she had been subject to high blood-pressure for a great many years. On examination, the reading was 220 systolic, 110 diastolic. The heart was somewhat enlarged; a loud systolic murmur was distinctly heard in the aortic area and was transmitted to the vessels of the neck. The diagnosis was arteriosclerosis, myocarditis with anginal pains.

On April 14, 1925, a typical left cervical sympathectomy was performed under local anesthesia. There was no pain after the operation, and the blood-pressure was decidedly lower. Since then the patient has suffered from neuralgia of the left side of the head and left shoulder, but has not been incapacited thereby. She has been able to climb stairs without retrosternal discomfort.

Case 8. M. S., a woman fifty years old. The patient was first seen on April 13, 1925. In 1917, she had had a very severe attack of "flu" with shortness of breath and some cyanosis. This left her much debilitated. She had had attacks of migraine for years. In 1918, she had an operation for appendicitis.

In 1919, the patient had the first attack of angine. An X-ray taken at that time showed a slight enlargement of the arch of the aorta. There was some dullness to percussion. She was free from further attacks until about six months previous to admission, when she had a typical anginal attack. She had attacks more or less frequently since then,—five in all.

On examination, the findings showed the Wassermann test to be negative; the urine analysis, negative; hemoglobin, 75 per cent; coagulation time of the blood, two minutes.

The X-ray interpretation was as follows: There was considerable fibrosis and calcification at the roots of the lungs and the aortic knob was unusually prominent; but there was nothing in its appearance that would represent an abnormality in a patient of this age. The heart was within normal limits.

On April 14, 1925, a typical left cervical sympathectomy was performed. The patient left the hospital on the sixth day after the operation, and up to that time she had no return of the old pain. She was able to shop, go to the theatre, and climb stairs without the slightest discomfort.

Case 9. O. D., a man forty-three years old. The patient was first seen on September 19, 1925. The present illness began in March, 1925, with a severe attack of pain in the chest, radiating down the arm. The second attack, which was more severe than the first, occurred in July, 1925. At this time the patient was confined to his bed with fever and myocarditis. From then on, to the time of the operation, the attacks became more frequent and severe. He had never used nitroglycerine.

On January 4, 1926, a typical cervical sympathectomy was performed under local anesthesia. The patient was discharged from the hospital on the sixth day after the operation, having had no pain. Two weeks after the operation he returned to his office. One month after the operation he stated that he had had several reminders of the old pain, but that the attacks were not severe enough to require any medication. The pain was never referred down the arm.

On July 12, 1926, the patient died very suddenly of acute dilatation of the heart. Almost complete relief.

Case 10. N. L. C., a man sixty-four years old. The patient was first seen on November 16, 1925. The first attack of angina had occurred in July, 1925. Since then he had been having three or four light attacks a day and about two severe attacks a week. The pain was vice-like in character in the lower chest and radiated down both arms. The examination at the time of the first visit showed a widened aortic shadow; the electrocardiogram was normal.

On January 12, 1926, under local anesthesia, the left cervical sympathetic ganglion was removed.

On January 13, 1926, under local anesthesia, the right cervical sympathetic ganglion was removed.

The patient was entirely free from pain for about one week. From then on until the time of his death, July 19, 1928, he had reminders of the pain, but it was not as severe and did not radiate down the arms. He died suddenly two years and six months after operation, apparently from apoplexy. Partial relief.

Case 11. L. E. W., a man sixty years old. The patient had always been very healthy and active until the first attack of pain in 1924. He was first seen on February 12, 1926, when he gave a history of having had severe attacks of angina

for two years. The attacks were becoming worse and occurred more frequently. The examination was negative, except for an elevation of the blood-pressure.

On February 15, 1926, under local anesthesia, the left superior cervical sympathetic ganglion was removed. The patient had a severe attack of pain just following the operation; but from then on, the attacks of pain were very mild, rarely requiring the use of nitroglycerine. He was able to walk three or four blocks without discomfort.

On April 26, 1928, there was a recurrence of the old pain, which was controlled only by large doses of morphine. On the following day there was evidence of impairment of the heart-action; and the heart-sounds gradually became weaker, until he died on April 28, 1928, of myocardial insufficiency,—two years and two months after the operation. Partial relief.

Case 12. R. A., a man sixty-one years old. The patient was first seen on February 15, 1926. His past history was negative. On December 20, 1924, he had the first attack of anginal pain. After that, any excitement or exertion brought on the same severe pain, which was relieved only by nitroglycerine. On examination he showed a Corrigan pulse, aortic regurgitation, mitral insufficiency, cardiac enlargement to the left and right. He was put to bed for three weeks. During this time he suffered almost constantly from severe pain.

On March 15, 1926, under local anesthesia, the right cervical sympathetic ganglion was removed. The patient had severe pain during the operation until the ganglion was isolated and its attachments were cut. The pain then ceased immediately. He returned to his room in excellent shape. One half hour after the operation he complained of shortness of breath and died before aid could reach him.

A partial autopsy was performed. The lungs appeared to be normal; the aorta, markedly atheromatous and not dilated. The aortic valves were incompetent and sclerotic; and the myocardium showed distinct changes. The most marked findings, however, were in the coronary arteries. These were extremely brittle, but not thrombosed. Death.

Case 13. J. Q., a man forty-seven years old. The patient was first seen on March 19, 1926. He had always been well and healthy until five years before, when he had had the first attack of pain in the chest and left arm. After that time he was comparatively free from pain for two years, when he had another severe attack. From then on, until the time of examination, any exertion, excitement or the ingestion of food brought on an attack of pain. The examination was essentially negative. The blood-pressure was 110.

On March 23, 1926, under local anesthesia, a right cervical ganglionectomy was performed. The patient has had no severe attacks since the operation, and scarcely ever takes nitroglycerine. He has gained about 30 pounds and is able to walk up two flights of stairs without discomfort. Almost complete relief.

Case 14. C. H., a man fifty-four years old. The patient was first seen on April 20, 1926. He had always been strong and vigorous. In November, 1925, he had a slight attack of pain in the chest. In January, 1926, he had a typical severe attack of angina. The examination at that time revealed a blood-pressure of 160; the chest was negative; the Wassermann test was negative; the blood-chemistry showed high protein nitrogen, some increase in uric acid and creatine. After two weeks in bed, the blood-pressure was reduced to 146. During this time the patient had no attacks of pain.

On April 22, 1926, a left superior cervical sympathectomy was performed. In spite of the careful identification of the nerves, there was an immediate change in the voice upon the removal of the ganglion, but no pronounced Horner's syndrome. Several days later the palate and pharynx showed marked edema and paralysis of the left vocal cord. It was thought that the vagus nerve had been injured. Two weeks after the operation, the patient had an attack which was diagnosed by the cardiologist as a partial coronary thrombosis.

On October 19, 1926, the patient had had no pain except a slight burning sensation occasionally, after eating. His voice was markedly improved.

In September, 1928, there was still no pain, and his voice was practically normal. The pupils reacted, and there was no enophthalmos. On examination, the heart was normal; the blood-pressure, 170 systolic, 114 diastolic. Almost complete relief.

Case 15. M. V. B., a woman sixty-four years old. The patient had always been well and healthy. About six months previously she had had the first attack of retrosternal pain, extending down the left arm. From then on, to the time of the operation, the pain became more severe and the attacks more frequent.

On June 19, 1926, a left cervical sympathectomy was performed under local anesthesia. The patient had no recurrence of the pain, but developed weakness, shortness of breath and irregular heart-action. She died about one month after the operation. There was no autopsy. Relieved.

Case 16. L. S., a woman fifty-seven years old. The patient had always been well and healthy. She was first seen on October 11, 1926. At that time she had been having pain in the right chest and arm, upon excitement or exertion. The examination showed an aortitis; the heart and aortic arch were enlarged. There was a left systolic murmur; the blood-pressure was 175 systolic, 90 diastolic.

On November 8, 1926, the right cervical sympathetic ganglion was removed under local anesthesia.

On May 11, 1927, the patient reported two severe attacks of pain after undue exertion, which were promptly relieved by nitroglycerine.

In July, 1928, she died of myocarditis. Good partial relief.

Case 17. A. F., a man fifty-five years old. The patient was first seen on March 8, 1928. He had always been well and healthy. The first attack of severe pain had occurred one year previously, lasting one hour and a half. At the time of the first visit, he had pain after each meal, after exercise or excitement. The examination was essentially negative.

On March 9, 1928, the right and left cervical sympathetic ganglia were removed under local anesthesia. During the operation the hypoglossal nerve was stretched.

On March 19, 1928, two attacks of substernal pain were reported,—since the operation.

By October, 1928, the attacks of substernal pain had become greatly lessened in severity and frequency, the hypoglossal palsy had entirely disappeared. Almost complete relief.

Case 18. O. A., a man seventy years old. The patient was first seen on March 8, 1928. He stated that twelve years previously he had had an attack of high blood-pressure, with resulting aphasia. He had recovered almost entirely from this condition. Four years prior to admission he had had the first attack of anginal pain. There had been a burning pain, a constriction of the chest, and pain in both arms. The attack had lasted four hours. Since then, he had had a number of

lighter attacks until August, 1928, when he had another severe attack, lasting thirty hours. He was then given nitroglycerine for the first time.

On examination the blood-pressure was 193 systolic, 100 diastolic. There was aortic tension, but not enough evidence in the electrocardiogram that the myocardium had been sufficiently damaged from possible attacks of thrombosis, to contra-indicate the operation.

On March 14, 1928, under local anesthesia, the right and left cervical sympathetic ganglia were removed.

On April 12, 1928, the patient suffered from a sense of suffocation, but there was no pain.

On August 3, 1928, it was reported by letter that he had had no pain since the operation; that he had developed diabetes and had been put on insulin. Complete relief.

Case 19. A. H. F., a man sixty-two years old. The patient was first seen on April 17, 1928. Six years previously he had had a prostatectomy; nine years previously he had developed diabetes, and at that time he had lost four toes from gangrene. He was able to control the diabetes by a restricted diet. The first attack of angina had occurred two months prior to admission, when he noticed pain across the right chest and right arm. This was brought on by walking or carrying a heavy bag. One month earlier he had had a very severe attack lasting thirty minutes. Despite the diabetes, the patient was considered a suitable case for operation.

On April 18, 1928, under local anesthesia, the right and left superior cervical ganglia were removed.

In October, 1928, the patient was reported to have had no severe attack of pain and only a feeling of distress in the chest. Partial relief.

Case 20. H. D., a man sixty years old. Appendectomy had been performed fifteen years previously, with good recovery. The first attacks of pain had started ten years previously. They were very slight in character and lasted only a second or two. The patient was first seen on July 17, 1928. At this time he was having severe attacks of angina, which were relieved only by the administration of nitroglycerine.

On September 18, 1928, he was seen again. The anginal attacks had become more frequent and more severe. He had been taking a great many depressant drugs, so that he was confused, excited and highly suspicious. He was oriented for persons, but not for time or place. He was admitted to a sanitarium for treatment for his mental condition.

On October 31, 1928, he was seen again. The anginal attacks were about the same as before. The mental condition had improved somewhat. An operation was advised and accepted.

On November 1, 1928, under general anesthesia, the superior cervical ganglion was removed. There was complete relief for forty-eight hours, then the pain returned in a milder degree. There was a typical Horner's syndrome. On account of the man's impatience, he was advised to submit to a stellate ganglionectomy from behind.

On November 8, 1928, under general anesthesia, the stellate ganglion was removed from behind. The patient has had some aching in the arms, but no anginal pain since the operation. Partial relief.

Part Two

HISTOLOGICAL STUDY OF THE CERVICAL SYMPATHETIC GANGLIA IN ANGINA PECTORIS[3]

JANVIER W. LINDSAY, M.D., E. CLARENCE RICE, M.D., AND MAURICE A. SELINGER, M.D.

IN STUDYING the tissues from patients in the present series, two features of the histological examination deserve especial comment. In the specimens from Cases 7, 8 and 16, in which no ganglion-cells were found, complete or partial relief from the symptoms is recorded. In Cases 9, 11, 12, 13, 18, 19 and 20, in which leucocytic infiltration was noted, partial or complete relief is recorded in five instances; in one case, the patient died immediately after the operation.

A comparison of these results with those reported in other cases, would indicate that the interruption of the nerve-tract gave practically the same result, at least for a considerable period of time, as did the removal of the ganglion. Presumably, however, the restoration of the continuity of the tract would be followed by a return of the symptoms of angina. There would also appear to be no distinct relationship between the evidence of the leucocytic infiltration of the ganglionic structures and the anginal attacks or the relief obtained.

It has not been possible to formulate any definite standard by which the relative proportion of connective tissue, as compared with the nerve-fibers and the ganglion-cells, may be determined as to its progressive increase with age or with the advance of the anginal process. For example, in Case 19, there was an unusual cellular abundance, even for a well-established case of angina.

The presence of a coarse, granular pigment deposit within the ganglion-cell capsule, was quite general in the series. At times it almost completely replaced the nerve-cells, although it was variable in extent and in the number of cells it involved. The same sort of deposit was also observed in the cells of the stellate ganglion from a three-year-old child who died of an acute infectious disease. This pigment was assumed to be that described by Ormos (40) and by

[3] From the Pathological Laboratory, Garfield Memorial Hospital, Washington, D. C.

others. It was considered to be lipoidal in character, but it evidently had no specific relation to angina.

The attempt to establish or to discover a relationship between the histological picture of the ganglia removed from patients suffering from angina pectoris and the occurrence or severity of the attacks, must be based upon the application of the principle pointed out by Nissl (38), emphasized by Paul Schröder (42), and embodied in the report of Clark (3); namely, the principle defined by the term, "equivalent picture." In other words, only when standardized and uniform methods are employed in the preparation of the tissues, from the very moment of their excision, can an interpretation of any value be expected.

The truth of this statement has been strongly impressed upon the authors by their own study of the cervical ganglia excised from nineteen cases of known angina, as well as by a comparison of the pictures observed in those instances with the reports and descriptions of other investigators (Clark (3), Oberndorfer (39), Ormos (40), Staemmler (46) and Terplan (47)). The specific relationship of pathological conditions in the ganglia, suggested by Ormos, seems at first to be a reasonable assumption from the discovery of the areas of leucocytic infiltration in the ganglia. The approximate estimation of the relative abundance of connective tissue, with a presumable reduction in the number of ganglion-cells in some instances and evidence of lipoidal degeneration in others, also lends support to this view. On the other hand, the consideration of the studies of the other investigators mentioned (Clark, Oberndorfer, Staemmler, Terplan), indicates that the same changes are regularly found in the ganglia from patients suffering from a great variety of other diseases, including many acute infections. In these cases, there has been no evidence of angina during life nor the suggestion of coronary or other vascular disease, at autopsy. One of the control cases in Clark's series was a boy ten years of age. In the ganglia from this child, areas of leucocytic infiltration were noted, but there were no other pathological changes. The authors have studied the stellate ganglion from a child about three years of age, who died of an acute infectious disease; but they found no particular pathological histology. In this instance, the same granular deposit, so emphasized by Ormos in connection with the anginal cases, was present in many of the cells. There appeared to be relatively less connective tissue in the ganglion of the child, however, than in the ganglia of the anginal cases observed by the authors.

It must also be borne in mind that a single control, such as that just described, is of little value until verified. Furthermore, great significance should be attached to the observation of Oberndorfer (39) that the conditions in the ganglia to which Ormos (40) has pointed, may be found in the ganglia of many persons of corresponding age, with no suspicion of angina. Of like importance is the work of Clark (3), who used many controls, including the ganglia of normal dogs.

The authors feel from their own study that the evidence supports chiefly the conclusion of Clark (3) that "no changes specific for angina pectoris have yet been demonstrated in the superior cervical sympathetic ganglia." In conducting future studies of this problem, investigators are urged to adopt Clark's careful system of controls and his consistent use of methods by which the "equivalent picture" of Nissl may be assured. Caution should be exercised against the interpretation of the histological study by the ordinary methods (such as those used by the authors), as affording conclusive evidence of the abnormality of the ganglia, whether specific or otherwise, in their relation to angina.

It is important to include in the controls, the ganglia from patients who are of an age at which angina pectoris is common, yet who are known not to have suffered from the disease, and in whom are found the vascular changes ordinarily associated with anginal attacks. As such material must obviously be obtained postmortem, careful consideration should be given the possible alterations occurring between death and the necropsy. In the present cases of ganglionectomy, the autopsy material has been so limited that conclusions regarding this phase of the subject are not warranted at the present time. The examination of the excised ganglia should, however, be made a part of the study of the angina problem; just as the histology of excised tissue is a recognized part of the general understanding of any other problem in question.

CASE REPORTS

HISTOLOGICAL EXAMINATION AND CLINICAL RESULTS[4]

Case 1. A. M. W. Operation: 1924. Superior cervical ganglia, left and right. (*L*) Apparently nerve-fibers and groups of nerve-cells. (*R*) Nerve-fibers and groups of nerve-cells. Almost complete relief.

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[4] For detailed reports of these cases, see pp. 770–777.

Case 2. W. E. P. Operation: March, 1924. Superior cervical ganglion, left. Miscropically showed typical ganglion-cells arranged in larger and smaller groups separated by strands and bundles of nerve-fibers and connective tissue. Complete relief from anginal attacks. Died four years after the operation, without recurrence of pain.

Case 3. R. H. Operation: March, 1924. Superior cervical ganglion. Typical ganglion structure, without particular pathological features. Complete relief.

Case 4. E. B. P. Operation: October, 1924. Nerve-fibers and groups of nerve-cells. Diagnosed sympathetic ganglion and nerve-fibers. Another portion of excised tissue was of nerve-fibers with no ganglion-cells. Patient died shortly after the operation.

Case 5. C. H. F. Operation: March, 1925. Superior cervical ganglion, left. Fibrous connective tissue in which were imbedded large groups of ganglion-cells. Practically complete relief, until a single attack of the "old pain" on November 12, 1928.

Case 6. T. E. M. Operation: March, 1925. Superior cervical sympathectomy, left. No histological examination. Reported as having "good relief" in November, 1928.

Case 7. G. D. Operation: April, 1925. Superior cervical sympathectomy, left. Nerve-fibers with connective tissue. No ganglion-cells. Complete relief.

Case 8. M. S. Operation: April, 1925. Cervical sympathectomy, left. Nerve-fibers. No ganglion-cells. Complete relief reported in December, 1927.

Case 9. O. D. Operation: January, 1926. Superior cervical sympathectomy, left. Typical ganglion structure, with extensive congestion. Complete relief. Patient died suddently in June, 1926.

Case 10. N. L. C. Operation: January, 1926. Superior cervical ganglion, left. Typical ganglion, with many typical cells. There was congestion of the tissues at one side of the section (traumatic); and several areas of round cell (leucocytic) infiltration were seen.

Superior cervical ganglion from the right side showed practically the same histological picture as the left. Partial relief. Died suddenly in July, 1928.

Case 11. L. E. W. Operation: February, 1926. Superior cervical ganglion, left. Typical nerve-ganglion, with occasional small area of inflammatory reaction, as indicated by leucocytic infiltration. Partial relief. Died, April 26, 1928, from myocarditis.

Case 12. R. A. Operation: March, 1926. Superior cervical ganglion, right. Typical nerve-ganglion structure, rich in nerve-cells, with occasional small area of leucocytic infiltration. Died suddenly, following the operation.

Case 13. J. Q. Operation: March, 1926. Superior cervical ganglion, right. Nerve-ganglion structure, with rather diffuse leucocytic infiltration. Complete relief.

Case 14. C. H. Operation: April, 1926. Ganglion nodosom could not be differentiated from sympathetic ganglion histologically.

Case 15. M. V. B. Operation: June, 1926. Superior cervical sympathectomy, left. Typical ganglion structure, with markedly dilated blood-vessels in many areas. Relieved. Died one month after operation from myocarditis.

Case 16. L. S. Operation: November, 1926. Superior cervical sympathec-

tomy, right. Sections showed only portions of nerve-fiber and its sheath. No ganglion-cells. Partial relief. Died in July, 1928, from myocarditis.

Case 17. A. F. Operation: March, 1928. Superior cervical ganglia, right and left. Typical nerve-ganglion structure, with fibrous capsule and congested vessels. Almost complete relief.

Case 18. O. A. Operation: March, 1928. Superior cervical ganglia, right and left. Typical nerve-ganglion structure, without evidence of leucocytic infiltration. Complete relief. Developed diabetes.

Case 19. A. H. F. Operation: April, 1928. Superior cervical ganglia, right and left. Typical ganglion structure, with definite congestion and several areas of leucocytic infiltration, generally perivascular. Partial relief.

Case 20. H. D. Operation: November, 1928. Superior cervical ganglia, right and left. Both ganglia showed the usual microscopic structure, with a rather unusual abundance of ganglion-cells. There was marked congestion and a number of areas of leucocytic infiltration were seen. Partial relief.

DISCUSSION

The following questions submitted to Dr. Kerr before the Commission, together with the answers to them, are here reported verbatim.

Dr. Frazier: I should like to ask Dr. Kerr whether he thinks sufficient afferent impulses pass through the left superior cardiac nerve to justify the Coffey-Brown operation (4–6) as a primary procedure in practically all cases?

Dr. Kerr: My experience being limited to one case of the more elaborate and complete operation of Jonnesco (23–29), I am not in a position to make a comparison. The large percentage of relief obtained in these twenty cases, compared with the reports of the relief obtained by the more elaborate and more dangerous operation, leads me to believe that just as good results can be obtained by the simple procedure.

Dr. Reid: Why should the superior cervical ganglion be removed when a section of the cervical sympathetic trunk will interrupt as many cardiac fibers as will the removal of the ganglion?

Dr. Kerr: The ganglion was removed because of our uncertainty as to the regeneration of the sympathetic fibers.

Dr. Kennedy: Would Dr. Kerr operate upon all cases of angina pectoris, or is there a method of selection?

Dr. Kerr: The cases that come directly to me, are always referred to a cardiologist. I have left it to him to determine whether they are suitable for operation or not. One or two cardiologists in Washington are now sending me cases that they did not feel were suitable for operation when first seen. We have operated with satisfactory results, upon cases that have had attacks of coronary thrombosis and upon cases with associated cardiac disease, sometimes with decompensation.

Dr. Rabiner: If we assume that pain is a danger signal in angina pectoris, may we not be creating some element of harm to the patient by removing that danger signal?

Dr. Kerr: If we interpret the occurrence of pain to mean the occurrence of spasm and if we break the reflex arc, that not only prevents the patient from feeling the pain but also prevents the spasm; so we are doing the patient good rather than harm.

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CHAPTER XXXV

ANGINA PECTORIS[1]

Relief from Pain by Paravertebral Alcohol Block of Upper Dorsal Sympathetic Rami

JAMES C. WHITE, M.D.

ANATOMY AND PHYSIOLOGY OF CARDIAC NERVES

FOLLOWING the work of Langley (16) it is generally believed that the sympathetic sensory and motor nerve-supply to the heart and ascending aorta is derived from the upper dorsal segments of the spinal cord. Both afferent and efferent fibers cross from the cord to the prevertebral sympathetic ganglia by the white rami communicates (Fig. 182). The cervical nerves possess the gray rami only and therefore are not concerned with cardiac pain; while from the sixth dorsal nerve down the sympathetic fibers enter the splanchnic nerves to the abdominal viscera. There is still, however, no unanimity of opinion as to how the cardiac motor and sensory fibers pass from the upper dorsal sympathetic trunk to the heart and therefore how best to interrupt them surgically.

In accordance with the ideas of François-Franck (8), most surgeons have operated upon the cervical sympathetic trunk. Jonnesco (14) felt that its complete removal, from the stellate to the superior cervical ganglion, was harmless and would cause a complete sensory-motor denervation of the heart. Danielopolu (6), however, has stated that it is unsafe to cut the cardiac accelerator fibers which he assumes all pass through the stellate ganglion and the inferior cardiac nerves. Following his suggestions Leriche (17), Hofer (10), and most of the other European surgeons, have limited their operations to cutting the upper rami of the stellate ganglion to the brachial plexus, the vertebral nerve, and more or less of the upper cervical sympathetic trunk with its branches which descend into the thorax or anastomose with the vagus. In this country Coffey and Brown (4) have felt that by

[1] From the Cardiac Clinic and West Surgical Service, Massachusetts General Hospital, Boston.

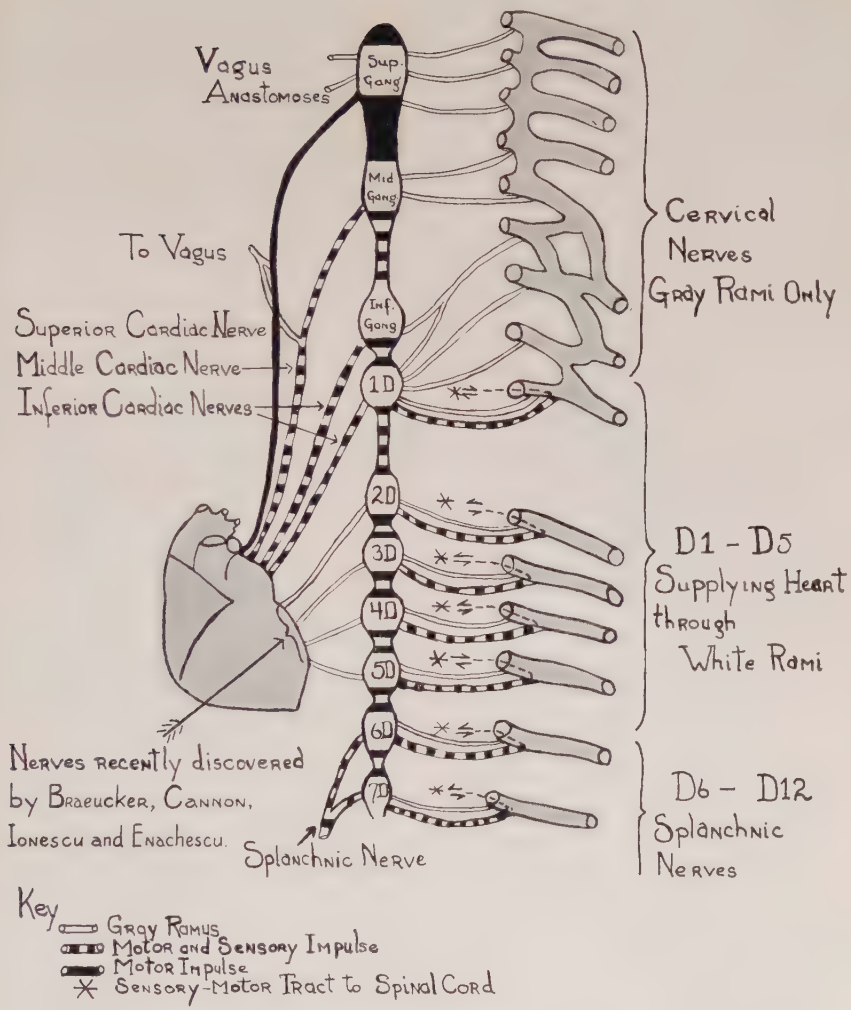


FIG. 182. Diagram showing the connections joining the central nervous system with the cervico-dorsal sympathetic trunk, and the nerves running from the trunk to the heart. The nerves described by Braeucker (1), Cannon and others (2), Ionescu and Enachescu (13), connecting the upper dorsal ganglia directly with the heart, are sketched in outline, as it is not yet definitely known whether they are sensory as well as motor. The motor nerves are represented by the solid black lines; the combined motor-sensory nerves by the black and white lines; and the gray rami by the white lines.

removing only the superior cervical ganglion they were able to relieve anginal attacks with a minimum of surgery. Holmes and Ransom (11) believe that this operation interrupts vasoconstrictor fibers running in the superior cardiac nerve to the coronary arteries. Subsequent results have proved that this limited procedure is not nearly so effective as the more extensive removals of the lower cervical sympathetic nerve employed in Europe. But no matter which of these operations is used, it is almost impossible to disconnect all of these tracts by any operation limited to the neck, because of the numerous anastomoses of the cardiac nerves in the neck with each other, with the inferior laryngeal nerve and the vagus, not to mention other frequent anatomical variations. The author believes that this fact accounts for the lack of uniform results reported in the literature of surgery in angina pectoris.

Recent anatomicophysiological research has shown that all these operations have further defects. Braeucker (1), in Hamburg, and Ionescu and Enachescu (13), in Bucharest, have demonstrated direct postganglionic connections between the upper thoracic sympathetic trunk and the heart. This finding has been corroborated from the physiological point of view by Cannon, Lewis and Britton (2), who have shown that the heart-rate can still be accelerated after the excision of both stellate ganglia, even when connections with both vagi and both adrenal glands have been removed. It has been demonstrated that cardiac acceleration in the cat is completely lost only when the rami of the upper five to six dorsal nerves have all been cut. (Fig. 182; see also p. 756.)

On the purely sensory side Spiegel (22), in Vienna, has shown that removal of the upper cervical sympathetic nerve in a dog has no effect in blocking the pain produced by stretching the ascending aorta. This can be relieved only by removing the stellate ganglia or by dividing the rami of the upper five dorsal nerves.[2]

With these points in mind, the question arises as to the best way to block the pain of angina pectoris. It is known that the left-sided pain

[2] The author has purposely not discussed the rôle of the vagus nerve in angina pectoris. There is fairly good evidence that this nerve is not implicated in the attacks, since its motor function is purely depressor; and there are several reports of its having been cut or blocked on the left side during the course of an attack without any subsequent relief from pain. Hofer (10), who has frequently cut the depressor branch of the vagus nerve, has recently given up this limited procedure.

is referred from the heart to the upper five segments of the dorsal cord, that its chief conduction-path is via the inferior cardiac nerves and the stellate ganglion to the upper thoracic chain, that a part probably descends the lower cervical sympathetic trunk from the middle cardiac nerve, and that a third portion may cross directly from the heart to the upper dorsal ganglia. From these ganglia the pain-fibers enter the left dorsal nerve-roots by the white rami communicantes.

As pointed out by Mackenzie (18), Langley (16), and Swetlow (23), no operation limited to the cervical sympathetic branch, can cut all these pathways.

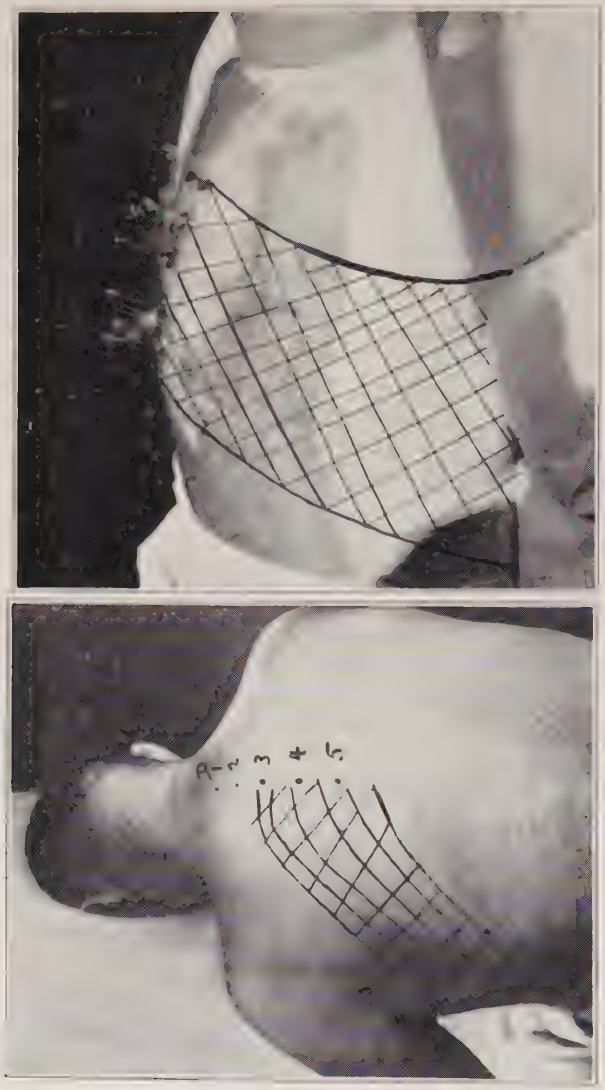
CLINICAL STUDIES

It can be shown from the foregoing summary of the present knowledge of cardiac enervation, that there are three surgical procedures which are theoretically capable of blocking all the cardiac pain-tracts to the spinal cord: (*a*) removing the stellate ganglion, with the upper five thoracic sympathetic ganglia; (*b*) cutting or blocking the corresponding rami communicantes; and (*c*) cutting the corresponding posterior spinal nerve-roots.

The third is the only method which preserves the cardiac accelerator tracts. The author and his colleagues are planning to try this procedure whenever they have a patient who presents a suitable surgical risk. The excision of the prevertebral sympathetic ganglia has become a surgical possibility by the approach described by Adson and Brown for the excision of the stellate and second dorsal ganglia in Raynaud's disease.[3] The author has recently used it in a case of severe angina pectoris in a man, aged twenty, with aortic regurgitation but with good heart-muscle. In this instance the operation has apparently afforded complete relief from the painful attacks, but it is much too severe a surgical procedure to be employed in the usual case of angina pectoris.

The second method mentioned is by far the easiest to carry out. It can be done either by direct cutting of the white rami or by paravertebral injection. Injection was first performed by Mandl (19) in Vienna, in 1924, with procaine hydrochloride. All the injections gave relief, but the cessation of pain varied from only a few hours to eleven months. This method is still in use in Vienna. The

[3] This volume, pp. 721–765.



A *B*

FIG. 183. Photograph of the back of the patient in Case 1, showing *A*, the points of injection 4 cm. to the left of the spinous processes, and the characteristic anesthesia. The descending cervical nerves overlap and obscure the anesthesia of the upper two or three segments. This man showed a typical Bernard Horner syndrome as well. *B*, the back of the same patient in final right-sided injection, when D5 to D7 were injected. The cross-hatched lines mark the posterior area of skin anesthesia. The five needles are in position.

author has tried procaine alone four times, and on each occasion obtained a respite for the patient which lasted thirty-six hours. The attacks then resumed their previous course.

Swetlow (23, 24) employed the same method, but used alcohol. His seventeen reported cases have shown results that compare most favorably with those obtained by radical operations. These reports are summarized (p. 798), with those of the author. Eleven injec-

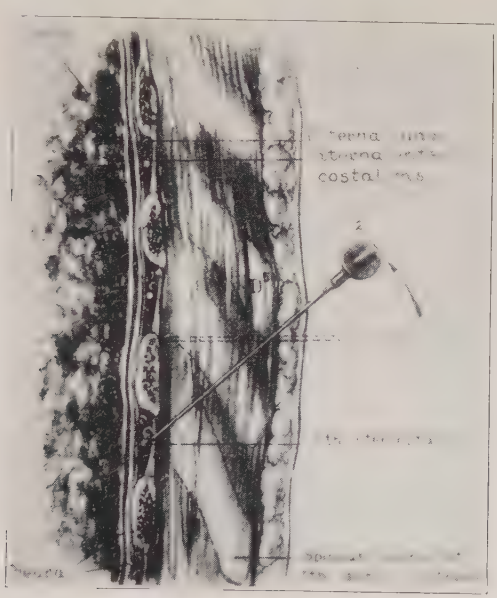


Fig. 184. Photograph showing technique of paravertebral injections: first position, needle taking contact with the rib; second position, after advancing needle beyond lower border of the rib into intercostal space (Labat (15), p. 266).

tions are reported from the Cardiac Clinic of the Massachusetts General Hospital; the first five were performed by the author (25) in 1927, and the others by Dr. W. J. Mixter in 1928.

TECHNIQUE OF PARAVERTEBRAL INJECTIONS

The technique of paravertebral injection used, is that described by Labat (15). For typical left-sided angina it is performed on the upper five left dorsal nerves just lateral to the intervertebral foramina.

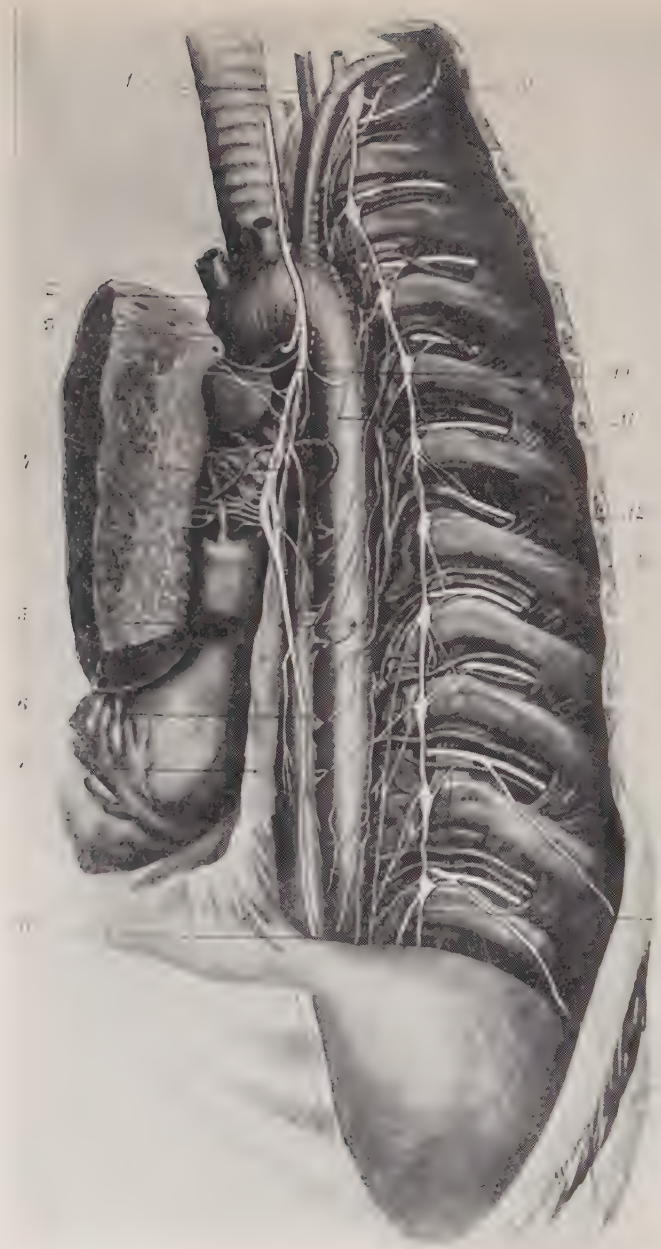


Fig. 185. Photograph showing dissection of the posterior mediastinum; and indicating the position of the intercostal nerves and sympathetic rami (Hovelacque (12)).

Briefly, it consists in having the patient lie on his left side with his legs drawn up as for a lumbar puncture. The back is painted with iodine and the spines of the upper five dorsal vertebrae palpated and marked with acriflavine (acriflavine on iodine gives a jet black sterile mark) (Fig. 183). Next, corresponding dots are made 4 cm. to the left of each dorsal spine. An intradermal injection of novocaine is made at each of these points. Through each wheal a thin needle (8 to 10 cm.), not attached to a syringe, is advanced perpendicularly to the plane of the skin. It should touch the upper border of the underlying rib. A few drops of novocaine are injected to desensitize the periosteum and the tip of the needle is shifted till it slips by the lower border of the rib. Its direction is then changed so that it points medially and toward the feet at an angle of 45 degrees (Fig. 184). Then it is pushed in exactly 2 cm. farther. It should now lie in the centre of the intercostal space near the artery, vein, and nerve, close to the point of origin of the sympathetic rami (Fig. 185). Aspiration suffices to prove that the needle has not punctured a blood-vessel or any abnormal prolongation of the subarachnoid space, while injection of a few drops of novocaine produces a cough-reflex if the pleura has been punctured. In either event no harm is done if the condition is recognized and the needle shifted. The author used five needles and injected 5 cc. of 1 per cent novocaine into each,[4] leaving all five in position. This should give a characteristic anesthesia of the chest-wall and axilla within ten minutes. If this does not appear the position of the needles must be corrected; whereas if anesthesia is complete, 5 cc. of 80 per cent alcohol are injected into each intercostal space and the needles withdrawn.

It should be emphasized that this is a fairly difficult and potentially dangerous procedure. The injection must be made within a few millimeters of the parietal pleura and close to the intervertebral foramen. It is therefore important to learn the technique thoroughly by preliminary injections of methylene-blue into the cadaver and to exercise extreme care in its clinical application.

SUMMARY OF CASES

In Table XVIII are summarized the clinical results of the paravertebral alcohol injections. All of these patients were selected by Dr. Paul D. White as being the most severe and obstinate cases of angina pectoris coming to the cardiac clinic. None were refused on account of being too sick, although many had angina at complete rest in bed, and had had previous attacks of coronary thrombosis.

[4] Five cubic centimeters of alcohol causes an area of necrosis about 1 cm. in diameter, whereas 5 cc. of novocaine diffuses over a much wider area, and may produce anesthesia beyond the zone to which the alcohol can penetrate. Some of the failures to secure a complete block with alcohol after a successful novocaine injection are probably due to this fact. Hereafter, the author intends to inject only from 1 to 2 cc. of 2 per cent novocaine, a procedure which will require a much closer contact with the intercostal nerve.

TABLE XVIII

CASES TREATED BY PARAVERTEBRAL ALCOHOL INJECTION AT THE MASSACHUSETTS GENERAL HOSPITAL

CASE NO.	AGE	DIAGNOSIS	TREATMENT	RESULTS	DEGREE OF RELIEF	DURATION	STATUS AT LAST REPORT
					per cent		
1	54	Syphilitic aortitis, aortic regurgitation; hypertension; angina pectoris; confined to bed	Left 2/19/27 Right 3/20/28	Left-sided relief; development of right-sided pain; no relief	100 (left side) 0* (right side)	To date	Up and about but unable to work. Moderate attacks of right-sided pain
2	60	Hypertensive and arteriosclerotic heart disease; aortic regurgitation; angina pectoris; previous attack of coronary occlusion; slight congestive failure	Left 5/16/27 Re-injection 6/23/27	Considerably relieved; further relief	50	To death	Able to resume light work until sudden death, undoubtedly from coronary thrombosis or angina pectoris, Feb. 8, 1928. No autopsy
3	53	Arteriosclerotic heart disease; hypertension; angina pectoris at rest	Left 6/9/27	Relief slight but definite; difficult to judge because of extreme nervousness	20	To date	Up and about, quietly active, appearing in good health but with moderate angina pectoris, Nov., 1928
4	54	Moderate arteriosclerosis and enlarged heart; angina pectoris; incapacitated	Left 7/22/27	Left-sided relief; mild right-sided attacks	100	To date	In fair health, but still has right-sided angina pectoris; has resumed work as truck driver

5	59	Arteriosclerotic heart disease; hypertension; myocardial insufficiency; previous coronary thrombosis	Left 8/12/27	Partial relief	25*	To death	Died suddenly, Jan. 9, 1928, undoubtedly of coronary thrombosis or angina pectoris. No autopsy
6	52	Hypertensive heart disease; aortic regurgitation; angina pectoris at rest	Left 11/5/27	Complete relief at first, later slight recurrence	100 90	To date	Comfortable and able to do light work, Aug. 1, 1928
7	58	Arteriosclerotic heart disease; hypertension; angina pectoris	Right 3/3/28	Considerable relief	65	To date	Fairly comfortable and has resumed light work, Aug., 1928
8	68	Arteriosclerotic heart disease; hypertension; angina pectoris; previous coronary thrombosis	Left 4/17/28	Partial relief at first, then recurrence. Judgment of case somewhat difficult because of nervousness	75 50	To date	Uncomfortable, angina pectoris daily but able to be quietly up and about, July, 1928
9	47	Hypertension arteriosclerosis; coronary thrombosis; angina pectoris; confined to bed	Left 9/4/28	Complete relief from attacks	100	To death	Died of myocardial failure with angina, Nov. 4, 1928
10	51	Arteriosclerotic heart disease; coronary thrombosis; angina pectoris; morphinism	Left 9/14/28	Relief from attacks		To death	Five days later another attack of coronary thrombosis. Died, Oct. 4. Died too soon to be included in series.

* Inadequate anesthesia from alcohol. Poor result probably due to failure in technique.

Few comments are necessary. The poor results of injection into the right side in Case 1 and into the left side in Case 5 can be accounted for by the failure to secure a lasting anesthesia with the alcohol (sensation over the peripheral distribution of the injected spinal nerves returned after the effect of the novocaine had worn off). Case 3 is that of a Jewish woman so nervous that no one has been able to ascertain how much of the pain of which she now complains, is anginal. The second patient was pleased with the result for six months. There was then a recurrence of anginal attacks with increasing severity until death occurred during an attack nine months after injection. In Cases 9 and 10 the injections were made during the course of severe anginal attacks and it was interesting to note that in each instance the symptoms ceased abruptly as the injection was made into the third dorsal nerve.

It was not expected that complete relief would last for more than six months; but the first patient has not had an attack of pain on the right side for over twenty-two months. The Bernard-Horner syndrome in this case lasted a year. The contracted pupil and narrowed palpebral fissure following injection is a very good sign and has been present in two out of three of the cases who have shown 100 per cent relief. The skin anesthesia of the chest-wall, on the other hand, usually lasts only a few weeks and is then replaced by hyperesthesia which lasts for nearly a month. This is always more or less troublesome; in one instance the patient complained that it was as bad for a week as the angina had been. Two cases had mild pleuritic pain for twenty-four hours after injection and one an alarming left-sided pallor of the face and low blood-pressure for an hour, but there were no more serious accidents. The fact that four of the patients have since died is not surprising in view of the severity of the cases treated.

COMMENT

To employ radical treatment for angina pectoris is obviously playing with fire. One of Swetlow's prospective patients died the night before it had been planned to make an injection. Danielopolu (4), Hesse (9) and Leriche (17) claim that blocking the accelerator nerves can be done safely in normal persons but that it is very dangerous in patients with angina pectoris. These investigators pointed to the 19 per cent of early mortalities in the Jonnesco operation (14), from acute

decompensation and pulmonary edema. On the other hand Cutler (5) and Cannon, Britton and others (3) have shown that dogs and cats can stand the removal of both the stellate ganglion and (in the latters' cats) the entire upper sympathetic chain on both sides as well. These animals still respond to exercise by a rise in pulse-rate from the effect of adrenalin and a checking of the inhibitive impulses of the vagus. This question is certainly an important one and requires careful study. The author's cases have shown no tendency to early cardiac decompensation; and Case 1 (in an electrogram taken 20 months after injection) has exhibited a normal increase in pulse-rate with exercise and no evidence of further myocardial injury.

Another objection to the injection of alcohol paravertebrally is the proximity of the pleura to the spinal cord, but results to date show this danger is slight when one is experienced in the technique. The hyperesthesia of the chest-wall mentioned above seems to be unavoidable, and is always troublesome for several weeks.

In favor of this method are the following considerations: its simplicity in comparison with a radical operation; the slight degree of disability to the patient, who can resume his normal activity within a day or two; and the fact that it can be used with more comparative safety in severe cases of angina than could any form of operation. Some have objected that the effect of alcohol would be short lived, but the author has observed two cases who have now been completely relieved of pain for twenty-two and twenty-four months, respectively. This allows ample time for the nerves to regenerate if they are ever going to do so. As the rami communicantes are thin, finely myelinated structures, the author believes that with good injections the sensory paths can be permanently destroyed. Furthermore, if pain should recur, there is no contra-indication to a repetition of the injection; several of the patients have already requested this if they should have a severe recurrence.

In order to show the relative merits of paravertebral alcohol block and those of operation, the results in the cases treated by alcohol injections by Swetlow (24), Mixter and White (25) are compared with the operative statistics assembled by Richardson (21), Cutler (5), and Fontaine (7) (Table XIX). There is no question but that after operation the disability and the immediate postoperative mortality are both greater. Cutler had limited his percentage of operative deaths to cases that died in the first twenty-four hours, but the author

felt that four days is a fairer period to allow for the disintegration of a damaged heart. This has increased his figures for deaths after complete sympathectomy to 22.2 per cent, so that they agree more

TABLE XIX

RELATIVE MERITS OF PARAVERTEBRAL BLOCK AND OPERATION IN TREATMENT OF ANGINA PECTORIS

1. PARAVERTEBRAL INJECTIONS OF ALCOHOL

		MASSACHUSETTS GENERAL HOSPITAL	SWETLOW
Number of injections		11	17
Days in hospital		3–5	3–5
	per cent	*per cent*	*per cent*
Relief	100–90, 90–50 Good	40, 30 } 70	53, 35 } 88
	50–25 Improved	10	
	25– 0 Failures	20	12
Deaths		0	0

2. OPERATIONS FOR ANGINA PECTORIS

		TOTAL SYMPATHECTOMIES			PARTIAL SYMPATHECTOMIES		
		Massachusetts General Hospital	Cutler	Fontaine	Massachusetts General Hospital	Cutler	Fontaine
Number of operations		2	27	37	8	53	57
Days in hospital		7–12			7–12		
		per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Results	Good	50	63.0	57	37.5	41.5	66.7
	Improved		18.5	11		35.8	7.0
	Failures		7.4	8	50.0	11.2	10.6
	Unknown			5		4.0	5.2
Deaths		50	*11.1	19	12.5	7.5	10.5

*Postoperative mortality within the first twenty-four hours. Deaths within the first four days increased to 22.2 per cent, and compare more nearly with Fontaine's figures shown in Column 3.

closely with those published by Fontaine in his thesis (7). It shows, as Danielopolu (6) and Leriche (17) have pointed out, that this radical operation is extremely dangerous.

CONCLUSIONS

Much further work remains to be done in connection with the treatment by paravertebral alcohol-block both in perfecting the technique to enable accurate injection into the rami and in making sure that the heart is not injured by the blocking of its accelerator nerves. Much also remains to be investigated in the field of anatomical physiology of heart-enervation. For instance, it is not known definitely whether the relief of anginal attacks results from the blocking of the motor impulses or from the interruption of the sensory afferent tracts. As the two pathways are separated only at their point of entrance to the spinal cord, it is hoped to obtain some information by cutting the sensory tracts alone in the posterior roots,—provided a patient can be found with severe angina pectoris who is a good enough surgical risk to justify laminectomy.

Another matter for investigation regards the mechanism by which anginal pains are referred to the neck and jaw. It is not known at present what this mechanism is, nor whether dorsal block alone is capable of giving relief. Penfield (20) reported a patient who was completely freed from attacks in the chest and arm by the removal of the lower sympathetic cervical nerve; but the pain referred to the neck and jaw remained unchanged. Presumably, the injection of alcohol into the upper dorsal rami would not have been any more successful in relieving the condition, and this procedure would doubtless have had to be supplemented by a resection of the superior cervical ganglion.

In employing alcohol injections, just as in a successful sympathectomy, the best one can do for the patient is to rid him of his pain; one cannot thereby restore the diseased heart to a normal condition. But granted these limitations, the more one sees of alcohol injections, the more confident he becomes that this is a logical and safe method of treatment in severe forms of angina pectoris. The method in its present status gives promise of being distinctly less dangerous and of giving results that surpass those achieved by sympathectomy.

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LIST OF MEMBERS

ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE

May, 1930

Sustaining Members

*Amsden, George S., Psychopathic Department, Albany Hospital Albany, N. Y.
*Angell, Edward B., 295 Alexander Street, Rochester, N. Y.
*Armstrong, S. T., Hillbourne Farms, Katonah, N. Y.
*Ayer, James B., 475 Commonwealth Avenue, Boston, Mass.

Barker, Lewellys F., 1035 North Calvert Street, Baltimore, Md.
*Bascoe, Peter, 8 South Michigan Avenue, Chicago, Ill.
Block, E. Bates, Doctors Building, 478 Peachtree Street, Atlanta, Ga.
Brill, A. A., 15 West 70th Street, New York City
*Burr, Charles W., 1918 Spruce Street, Philadelphia, Pa.

*Cadwalader, William B., 133 South 36th Street, Philadelphia, Pa.
*Campbell, C. Macfie, 74 Fenwood Road, Boston, Mass.

D'Alton, Clarence J., 123 East 53rd Street, New York City

Ebaugh, Franklin G., 4200 East Ninth Avenue, Denver, Colo.
*Eckel, George M., Thompson Building, Hot Springs National Park, Ark.
Eckel, John L., 589 Delaware Avenue, Buffalo, N. Y.
*Elsberg, Charles A., 168th Street and Fort Washington Avenue, New York City

* Members present at the meeting in 1928.

*Farnell, Frederick, 598 Angell Street, Providence, R. I.
*Favill, John, 123 South Michigan Avenue, Chicago, Ill.
*Fox, James C., Sterling Hall of Medicine, Yale University, New Haven, Conn.

*Gregg, Donald, Wellesley, Mass.

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*Kauffman, Lesser, 584 West Ferry Street, Buffalo, N. Y.
*Kennedy, Foster, 410 East 57th Street, New York City

Mayer, Edward E., Medical Building, 3401 Fifth Avenue, Pittsburgh, Pa.
Mehrtens, Henry B., Stanford Hospital, Clay and Webster Streets, San Francisco, Calif.
*Mercur, William H., 5344 Fifth Avenue, Pittsburgh, Pa.
*Meyer, Adolf, Johns Hopkins Hospital, Baltimore, Md.
Meyers, I. Leon, 1930 Wilshire Boulevard, Los Angeles, Calif.
*Millet, John P., Stockbridge, Mass.
Mitchell, Harry W., State Hospital, Warren, Pa.
*Mixter, William J., 270 Commonwealth Avenue, Boston, Mass.
Myers, Glenn E., Professional Building, 1062 West 6th Street, Los Angeles, Calif.

Naffziger, Howard C., 384 Post Street, San Francisco, Calif.
Nathan, David, 1619 Spruce Street, Philadelphia, Pa.

*Oberndorf, C. P., 112 West 59th Street, New York City
*Ordway, Mabel D., 6 Parley Vale, Jamaica Plain, Boston, Mass.

* Members present at the meeting in 1928.

*Paton, Stewart, 3908 North Charles Street, Baltimore, Md.
*Patrick, Hugh T., 25 East Washington Street, Chicago, Ill.
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Redwood, Frank H., 142 West York Street, Norfolk, Va.
*Richardson, W. W., Mercur Sanitarium, Mercur, Pa.
Riggs, Austin Fox, Stockbridge, Mass.
*Riley, W. H., Battle Creek, Mich.
Russel, Colin, 900 West Sherbrooke Street, Montreal, Canada

*Sachs, Bernard, 116 West 59th Street, New York City
Sawyer, Carl W., White Oak Farms, Marion, Ohio.
Schaller, Walter F., 909 Hyde Street, San Francisco, Calif.
de Schweinitz, George Edmond, 1705 Walnut Street, Philadelphia, Pa.
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Sleyster, Rock, Wauwatosa, Wis.
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Strecker, Edward A., 345 South 19th Street, Philadelphia, Pa.

*Taylor, Edward W., 457 Marlborough Street, Boston, Mass.
*Terhune, William B., Stockbridge, Mass.
*Tilney, Frederick, 168th Street and Fort Washington Avenue, New York City
*Timme, Walter, 1 West 64th Street, New York City
Tucker, Beverly R., 212 Franklin Street, Richmond, Va.

*Van Epps, E. C., University Hospital, Iowa City, Ia.
Van Wart, Roy M., 3431 Prytania Street, New Orleans, La.

Waterman, G. A., 250 Beacon Street, Boston, Mass.
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*Wiedman, Otto G., 179 Allyn Street, Hartford, Conn.

*Zabriskie, Edwin G., 115 East 61st Street, New York City

* Members present at the meeting in 1928.

Active Members

Abrahamson, Isador, 129 East 69th Street, New York City
Adler, Herman M., 279 Mission Canyon Road, Santa Barbara, Calif.
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Amdur, Meyer K., Gallinger Municipal Hospital, Washington, D. C.
*Ames, Thaddeus H., 55 Park Avenue, New York City
*Aronson, Louis S., 268 West 91st Street, New York City

*Baines, M. Carroll, U. S. Veterans' Hospital, 130 West Kingsbridge Road, New York City
*Barrett, Albert M., State Psychopathic Hospital, Ann Arbor, Mich.
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Berens, Conrad, 30 East 40th Street, New York City
*Bernis, W. J., 5 Rowley Street, Rochester, N. Y.
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Blumgart, Leonard, 152 West 57th Street, New York City
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Brock, Samuel, 1192 Park Avenue, New York City
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*Brown, Sanger, 570 Park Avenue, New York City
Brush, Nathaniel H., 103 East Micheltorena Street, Santa Barbara, Calif.
Buckley, Albert C., Friends' Hospital, Frankford, Philadelphia, Pa.
*Bunker, H. A., Jr., Ward's Island, New York City
Burley, Benjamin T., 19 High Street, Worcester, Mass.
Burlingame, C. C., 622 West 168th Street, New York City
*Burr, Harold S., New Haven, Conn.

Canavan, Myrtelle M., Harvard Medical School, Boston, Mass.
Caner, G. Colket, 63 Morris Street, Boston, Mass.

* Members present at the meeting in 1928.

CANNADAY, ROYAL G., 45 East 62nd Street, New York City
*CARLISLE, CHESTER L., U. S. Veterans' Hospital, 130 West Kingsbridge Road, New York City
CARROLL, PATRICK M., 37 West 54th Street, New York City
*CARROLL ROBERT S., Highland Hospital, Asheville, N. C.
CASAMAJOR, LOUIS, 168th Street and Fort Washington Avenue, New York City
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CHURCH, ARCHIBALD, 1117 Marshall Field Annex, Chicago, Ill.
CLARK, L. PIERCE, 2 East 65th Street, New York City
*COBB, STANLEY, Harvard Medical School, Boston, Mass.
COLLIER, GEORGE K., 80 East Avenue, Rochester, N. Y.
*CORIAT, ISADOR H., 416 Marlborough Street, Boston, Mass.
*CORNWALL, LEON H., 40 East 61st Street, New York City
*COTTON, HENRY A., Station A, Trenton, N. J.
*CRAIG, C. BURNS, 129 East 69th Street, New York City
CRISPELL, RAYMOND S., 61 Wall Street, Kingston, N. Y.
CRAWFORD, A. S., Henry Ford Hospital, Detroit, Mich.
CROTHERS, BRONSON, 300 Longwood Avenue, Boston, Mass.
CURRIER, F. P., Grand Rapids Clinic, Grand Rapids, Mich.
*CURRY, MARCUS A., New Jersey State Hospital, Greystone Park, N. J.

DANA, CHARLES L., 53 West 53rd Street, New York City
DAVIDOFF, LEON M., 1049 Park Avenue, New York City
*DAVIS, LOYAL, 54 East Erie Street, Chicago, Ill.
*DAVIS, THOMAS K., 70 East 77th Street, New York City
DAVISON, CHARLES, 3066 Center Avenue, Pittsburgh, Pa.
DERCUM, FRANCIS X., 1719 Walnut Street, Philadelphia, Pa.
DOWMAN, CHARLES E., 158 Forrest Avenue, N. E., Atlanta, Ga.

ELWYN, ADOLPH, College of Physicians and Surgeons, 168th Street and Fort Washington Avenue, New York City
EMERY, E. VAN NORMAN, Sterling Hall of Medicine, Yale University, New Haven, Conn.
*ENGLANDER, CHARLES, 41 Hillside Avenue, Newark, N. J.

* Members present at the meeting in 1928.

Farrar, Clarence B., 50 Oride Gardens, Toronto, Canada
*Fay, Temple, 2025 Walnut Street, Philadelphia, Pa.
Fisher, Edward F., 46 East 52nd Street, New York City
*Folsom, Ralph P., Manhattan State Hospital, Ward's Island, New York City
*Frantz, Angus Macdonald, 58 East 65th Street, New York City
*Freeman, Walter, 1801 I Street, N. W., Washington, D. C.
*Friedman, E. D., 1192 Park Avenue, New York City

Gayle, Finley, Richmond, Va.
Gaines, Lewis M., 33 Forest Avenue, Atlanta, Ga.
Gibson, Edward T., 710 Rialto Building, Kansas City, Mo.
*Gillis, Andrew, C., 1033 North Calvert Street, Baltimore, Md.
Gilmore, Charles, Craig House, Beacon, N. Y.
Globus, Joseph H., 1075 Park Avenue, New York City
*Goodhart, S. Philip, 116 West 59th Street, New York City
Goodwin, Harold C., 111 Dickinson Street, Springfield, Mass.
*Gordy, Samuel T., Philadelphia Hospital for Mental Disease, Byberry, Pa.
Gosselin, George, 50 Farmington Avenue, Hartford, Conn.
Grant, Francis C., 133 South 36th Street, Philadelphia, Pa.
*Gregory, Menas S., 101 West 57th Street, New York City
*Grossman, Morris, 66 West 87th Street, New York City
Guion, Edward, Pleasantville, N. J.

Hanes, E. L., 748 East Main Street, Rochester, N. Y.
*Hamilton, Arthur S., 511 Yates Building, Minneapolis, Minn.
Harrington, Milton A., Dartmouth College, Hanover, N. H.
Harris, Titus, University of Texas, Galveston, Texas
*Haviland, Floyd, Manhattan State Hospital, Ward's Island, New York City
*Heldt, Thomas J., Henry Ford Hospital, Detroit, Mich.
Henninger, C. H., Jenkins Arcade Building, Pittsburgh, Pa.
*Henry, George, Bloomingdale Hospital, White Plains, N. Y.
Hill, Lewis B., The Sheppard and Enoch Pratt Hospital, Towson, Md.

* Members present at the meeting in 1928.

*Hinsie, Leland E., New York State Psychiatric Institute and Hospital, 722 West 168th Street, New York City
Hohman, Leslie B., Phipps Clinic, Johns Hopkins Hospital, Baltimore, Md.
Hodskins, Morgan B., Monson State Hospital, Palmer, Mass.
Horrax, Gilbert, 721 Huntington Avenue, Boston, Mass.
Hoskins, R. G., Harvard Medical School, Boston, Mass.
Howe, Hubert S., 115 East 61st Street, New York City
Huddleson, James H., 784 Park Avenue, New York City
Hughes, William Newton, 112 Waterman Street, Providence, R. I.
*Hunt, Edward Livingston, 41 East 63rd Street, New York City
Hunt, J. Ramsay, 46 West 55th Street, New York City
Hutchings, R. H., Utica State Hospital, Utica, N. Y.
*Hyslop, George H., 136 East 46th Street, New York City

*Ivimey, Muriel, 104 East 40th Street, New York City

Jacoby, J. Ralph, Hotel Bretton Hall, Broadway at 86th Street, New York City
*Jelliffe, Smith Ely, 64 West 56th Street, New York City
Johnson, George S., Colorado Psychopathic Hospital, Denver, Colo.
Jones, W. A., 406 Physicians and Surgeons Bulding, Minneapolis Minn.
Joughin, James L., 114 East 54th Street, New York City

*Kerr, Harry Hyland, 1744 N Street, Washington, D. C.
*Keschner, Moses, 32 West 82nd Street, New York City
Kilroy, Philip, 61 Chestnut Street, Springfield, Mass.
*Kirby, George H., Psychiatric Institute, Ward's Island, New York City
Kline, George M., Department of Mental Disease, State House, Boston, Mass.
Klingman, Theophil, St. Joseph's Sanitarium, Ann Arbor, Mich.
Knight, Augustus S., Metropolitan Life Insurance Company, 1 Madison Avenue, New York City
*Kraus, Walter M., 136 East 64th Street, New York City

* Members present at the meeting in 1928.

*Lambert, Charles I., 114 East 54th Street, New York City
*Lane, Arthur G., New Jersey State Hospital, Greystone Park, N. J.
Lang, H. B., Willard State Hospital, Willard, N. Y.
Langdon, Frank W., 4003 Rose Hill Avenue, Cincinnati, Ohio
*Leavitt, F. H., 1527 Pine Street, Philadelphia, Pa.
*Leahy, Sylvester R., 69 Remsen Street, Brooklyn, N. Y.
*Leiner, Joshua H., 355 East 149th Street, New York City
Lennox, William G., 47 Dudley Road, Newton Center, Mass.
*Levy, Milford, 2412 Eutaw Place, Baltimore, Md.
Lewis, Nolan D. C., St. Elizabeth's Hospital, Washington, D. C.
*Lorenz, William F., Psychiatric Institute, Madison, Wis.
Ludlum, Seymour De Witt, 1827 Pine Street, Philadelphia, Pa.
Lunt, Laurence K., Stockbridge, Mass.

McCarthy, W., 2025 Walnut Street, Philadelphia, Pa.
McConnell, J. W., 1904 Chestnut Street, Philadelphia, Pa.
McClintic, Clifton F., 1502 Stroh Building, Detroit, Mich.
*McDonald, Charles A., 106 Waterman Street, Providence, R. I.
McDonald, William, Jr., Marion, Mass.
McGaffin, Charles G., Randall's Island, New York City
*McKendree, Charles A., 114 East 54th Street, New York City
McKennan, T. M. T., Jenkins Arcade Building, Pittsburgh, Pa.
*McKinney, John M., 70 East 72nd Street, New York City
*Mackay, Fred H., 164 Crescent Street, Montreal, Canada
*MacPhee, John J., Wyoming Apartments, Seventh Avenue and 55th Street, New York City
MacRobert, Russell G., 944 Fifth Avenue, New York City
*Mailhouse, Max, 195 Church Street, New Haven, Conn.
Malamud, William, Foxborough, Mass.
Mason, V. R., 838 Pacific Mutual Building, Los Angeles, Calif.
*Mayer, W. H., 714 Jenkins Arcade Building, Pittsburgh, Pa.
Mella, Hugo, U. S. Veterans' Hospital, Palo Alto, Calif.
Menninger, Karl A., Mulvane Building, Topeka, Kansas
Michaels, J., Neurological Institute, 168th Street and Fort Washington Avenue, New York City
Mills, Charles K., 2121 Delancey Street, Philadelphia, Pa.

* Members present at the meeting in 1928.

Mills, George W., Superintendent, Brooklyn State Hospital, Clarkson Avenue, Brooklyn, N. Y.
Moersch, Fred P., Mayo Clinic, Rochester, Minn.
Moleen, George A., 324 Mack Block, Denver, Colo.
*Moore, J. Waldron, Beacon, N. Y.
Moren, J., 712 South 3rd Street, Louisville, Ky.
Muhl, Anita, 3578 Seventh Street, San Diego, Calif.
Murdoch, J. M., Station A, Faribault, Minn.
Myerson, Abraham, 483 Beacon Street, Boston, Mass.

Neal, Josephine B., Department of Health, Bureau of Laboratories, Foot of East 16th Street, New York City
*Neustaedter, M., 27 East 93rd Street, New York City
Nielsen, J. M., Battle Creek Sanitarium, Battle Creek, Mich.

Oliver, John R., Latrobe Apartments, Baltimore, Md.
Orbison, Thomas J., 2007 Wilshire Boulevard, Los Angeles, Calif.
Ornstein, A. M., 1629 North Franklin Street, Philadelphia, Pa.
*Orton, Samuel T., 66 East 79th Street, New York City
*Osnato, Michael, 121 East 60th Street, New York City
Osserman, H. A., 944 Park Avenue, New York City

Packard, Frederic H., McLean Hospital, Waverley, Mass.
Packer, Flavius, White Oak Farm, Pawling, N. Y.
Papez, James W., 101 Elmwood Avenue, Ithaca, N. Y.
*Pardee, Irving H., 160 East 64th Street, New York City
Parker, G. C., Hotel Plaza, New York City
*Parsons, F. W., Department of Mental Hygiene, Albany, N. Y.
Payne, Guy, Essex County Hospital, Cedar Grove, N. J.
Perkins, Orman, 829 Carroll Street, Brooklyn, N. Y.
Peterman, M. G., 167 Seventeenth Street, Milwaukee, Wis.
Peterson, Frederick, 20 West 50th Street, New York City
*Potts, Charles S., 2018 Chestnut Street, Philadelphia, Pa.
Pou, Robert E., 20 West 50th Street, New York City
†*Prince, Morton, 54 Devonshire Street, Boston, Mass.
Putnam, J. W., 525 Delaware Avenue, Buffalo, N. Y.

* Members present at the meeting in 1928.
† Deceased, 1929.

*Rabiner, A. M., 5 East 53rd Street, New York City
Rand, Carl W., 1034 Pacific Mutual Building, Los Angeles, Calif.
Raphael, Theophile, Psychopathic Clinic, Recorder's Court, Detroit, Mich.
*Raynor, Mortimer, Bloomingdale Hospital, White Plains, N. Y.
Riggs, C. Eugene, Hamm Building, St. Paul, Minn.
*Riley, Henry Alsop, 117 East 72nd Street, New York City
Rogers, Arthur W., Oconomowoc Health Resort, Oconomowoc, Wis.
Rosenheck, Charles, 100 Central Park West, New York City
*Rosett, Joshua, 100 Central Park South, New York City
Ross, Charles F., 1010 Schweiter Building, Wichita, Kansas
Royer, J. Elliott, 400 Twenty-ninth Street, Oakland, Calif.
*Russell, William L., Bloomingdale Hospital, White Plains, N. Y.

Sanborn, Harvey B., 112 Waterman Street, Providence, R. I.
*Sands, Irving J., 202 New York Avenue, Brooklyn, N. Y.
Savitsky, Nathan, Ward's Island, New York City
Schley, R. Montford, 74 Summer Street, Buffalo, N. Y.
Schwab, Sidney I., Humbolt Building, St. Louis, Mo.
Scott, Augusta, 149 East 40th Street, New York City
Sharp, Edward A., 81 Linwood Avenue, Buffalo, N. Y.
*Sheehan, R. F., 53 East 66th Street, New York City
Shockey, G. C., Melrose Park, Ill.
Silverman, Nathaniel E., 1070 Park Avenue, New York City
*Singer, H. Douglas, 300 North Michigan Avenue, Chicago, Ill.
Skoog, A. L., Rialto Building, Kansas City, Mo.
Sleeper, F. H., Worcester State Hospital, Worcester, Mass.
Solomon, Alfred P., 25 East Washington Street, Chicago, Ill.
*Solomon, Harry C., 270 Commonwealth Avenue, Boston, Mass.
*Spaulding, Edith R., 103 East 86th Street, New York City
*Spiller, William G., 4409 Pine Street, Philadelphia, Pa.
*Starr, M. Allen, 5 West 54th Street, New York City
Stearns, H. Warren, 520 Commonwealth Avenue, Boston, Mass.
†*Stephenson, Junius W., 20 West 50th Street, New York City
Stevens, Frank T., 211 Ferguson Building, Colorado Springs, Colo.

* Members present at the meeting in 1928.
† Deceased, 1929

Stevenson, George, 506 West 111th Street, New York City
*Stone, Theodore T., 55 East Washington Street, Chicago, Ill.
Stookey, Byron, 151 East 83rd Street, New York City
Strauss, Israel, 116 West 59th Street, New York City
Sullivan, H. S., The Sheppard and Enoch Pratt Hospital, Towson, Md.

*Thom, Douglas A., 520 Commonwealth Avenue, Boston, Mass.
*Thomas, J. J., 88 Bay State Road, Boston, Mass.
Thompson, W. N., Hartford Retreat, 400 Washington Street, Hartford, Conn.
Thompson, Lloyd J., Sterling Hall of Medicine, Yale University, New Haven, Conn.
*Tiffany, William J., State Hospital, Kings Park, N. Y.
*Trentzsch, Philip J., 1230 Park Avenue, New York City

Viets, Henry R., 8 Commonwealth Avenue, Boston, Mass.

Wagenhals, Franklin E., 1628 Richmond Avenue, Columbus, Ohio
*Waggoner, Raymond W., 726 Forest Avenue, Ann Arbor, Mich.
Wallace, Louis O. S., 36 Main Street, Suncook, N. H.
Wearne, Raymond G., Central Islip State Hospital, Central Islip, N. Y.
*Wechsler, I. S., 1112 Park Avenue, New York City
Weil, Arthur, 303 East Chicago Avenue, Chicago, Ill.
*Weinberg, Max H., 6097 Jenkins Arcade Building, Pittsburgh, Pa.
*White, William A., St. Elizabeth's Hospital, Washington, D. C.
*Wholey, Cornelius C., 4616 Bayard Street, Pittsburgh, Pa.
Williams, Tom L., Miami Beach, Fla.
Williams, Ward, 274 Alexander Street, Rochester, N. Y.
*Wilson, David Cole, University of Virginia, Charlottesville, Va.
*Winkelman, Nathaniel W., 319 South 18th Street, Philadelphia, Pa.
Witt, Samuel E., 158 West 58th Street, New York City
Witzell, August E., Brooklyn State Hospital, Clarkson Avenue, Brooklyn, N. Y.

* Members present at the meeting in 1928.

Wolff, Harold G., 355 West 246 Street, New York City.
Wolfsohn, Julian M., 490 Post Street, San Francisco, Calif.
*Woltman, Henry W., Mayo Clinic, Rochester, Minn.
Work, Philip, Metropolitan Building, Denver, Colo.
*Wright, George J., Jenkins Arcade Building, Pittsburgh, Pa.
Wright, W. W., 1565 Oneida Street, Utica, N. Y.

*Yaskin, Joseph C., 1832 Spruce Street, Philadelphia, Pa.

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